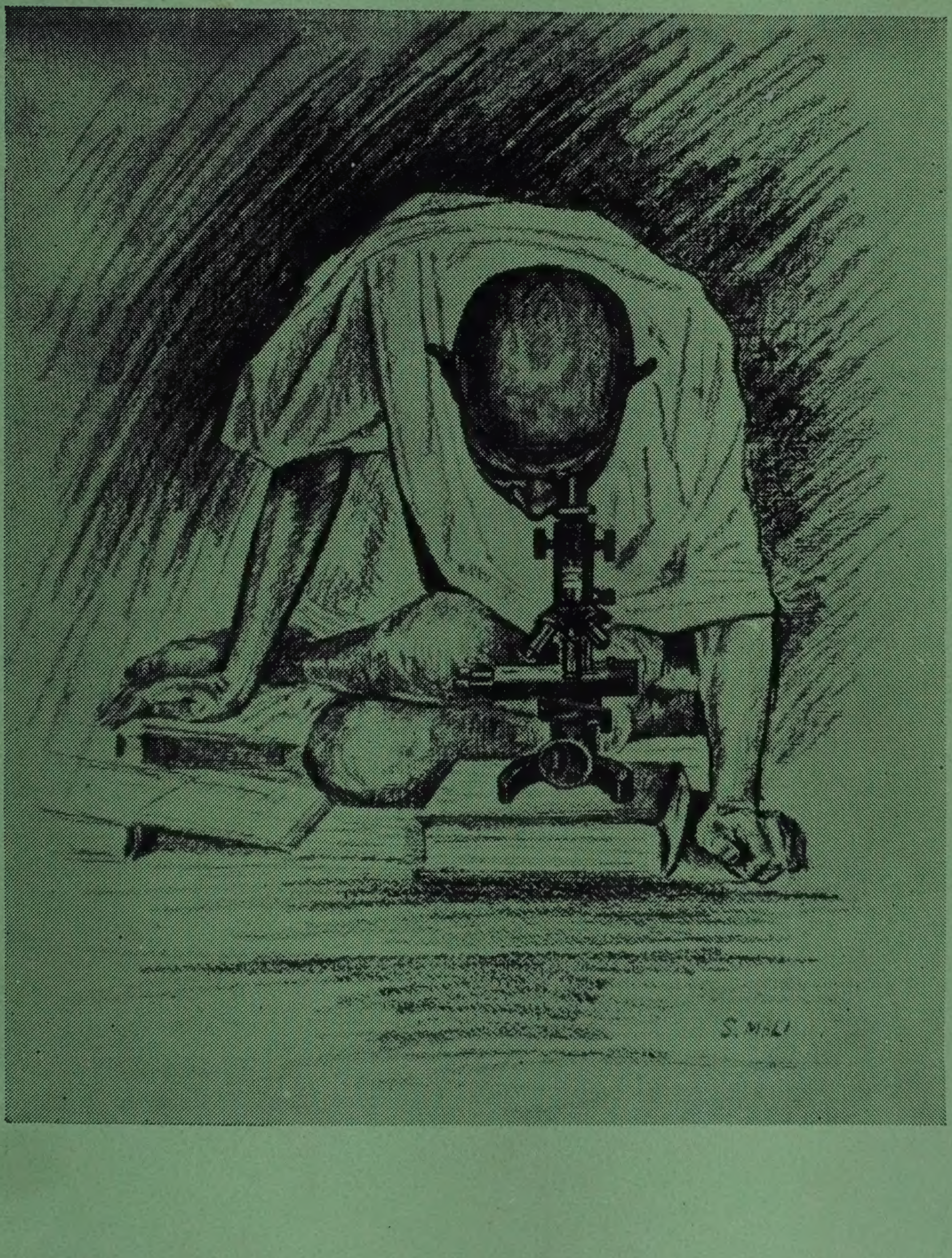
A WINDOW ON LEPROSY

GANDHI MEMORIAL LEPROSY FOUNDATION
SILVER JUBILEE COMMEMORATIVE VOLUME



Editor: B. R. CHATTERJEE

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LIST OF CONTRIBUTORS

M. ABE, M.D., National Institute for Leprosy Research, Higashi Murayamashi, Tokyo, JAPAN.

C. ANTONY SAMY, B.SC., D.M.I.T., M.S., Director, Workshop for Rehabilitation and Training of the Handicapped (WORTH), Katpadi Extension, Vellore 632006, INDIA.

A. D. ASKEW, M.A., International General Secretary, The Leprosy Mission, 50 Portland Place, London, WIN 3DG, U. K.

L. BECHELLI, M.D., Professor and Head of the Chair of Dermatology, Faculdade de Medicine de Ribeirao Preto, Rebeirao Preto, SP, BRAZIL.

B. BEIGUELMAN, M.D., Departamento de Genetica Medica, Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, SP, BRAZIL.

C. H. BINFORD, M.D., Division of Geographic Pathology, Armed Forces Institute of Pathology, Washington, D.C., U.S.A.

B. S. BLUMBERG, M.D., NOBEL LAUREATE, Institute for Cancer Research, Philadelphia, Pennysylvania, U.S.A.

S. G. BROWNE, M.D., FRCP, OBE, Director, Leprosy Study Centre, Secretary-Treasurer, International Leprosy Association, 57a Wimpole Street, London, WIM 7DF, U. K.

W. E. BULLOCK, M.D., Professor of Medicine, Director, Infectious Disease Division, College of Medicine, University of Kentucky, Lexington, Kentucky, 40506, U.S.A.

B. R. CHATTERJEE, M.B.,B.S., Director, Leprosy Field Research Unit, The Leprosy Mission, Member, Gandhi Memorial Leprosy Foundation, Jhalda, 723202, West Bengal, INDIA.

D. S. CHAUDHURY, M.B.,B.S., Director, Greater Calcutta Leprosy Treatment and Education Scheme (GRECALTES), 20 Broad Street, Calcutta, 700019, INDIA.

J. CONVIT, M.D., Director, Institute Nacional de Dermatologia, President, International Leprosy Association, Caracas, VENEZUELA.

T. F. DAVEY, M.D., Ch.B, M.Sc., C.B.E., Editor, Leprosy Review, 12 Garland Avenue, Emsworth, Hants, P010 7QA, U.K.

J. DELVILLE, Ph.D., Professor of Microbiology, Ecole de Sante Publique, Universite Catholique de Louvain, Bruxelles, BELGIUM.

K. V. DESIKAN, M.D., Director, Central JALMA Institute for Leprosy, Agra, 282001, INDIA.

DHARMENDRA, M.B.,D.BACT., Editor, Leprosy in India, A-2/50, Safdarjang Enclave, New Delhi, 110016, INDIA.

R. R. DIWAKAR, M.A., Ph.D., Chairman, Gandhi Peace Foundation, Din Dayal Upadhyay Marg. New Delhi, 110001, INDIA.

D. J. DRUTZ, M.D., Chief, Division of Infectious Diseases, Assoc. Professor of Medicine, The University of Texas Health Science Centre at San Antonio, Texas, 78284, U.S.A.

V. EKAMBARAM, M.B., B.S., Director, ELEP Leprosy Control Project, Dharmapuri, Tamilnadu, INDIA.

S. ESTRADA-PARRA, Ph.D., Institute Politecnico Nacional, Escuela Nacional Ciencias Biologicas, Mexico 17, D.F., MEXICO.

E. P. FRITSCHI, M.B., F.R.C.S., Superintendent and Consultant Surgeon, Schiffelin Leprosy Research Sanatorium, Karigiri, 632106, North Arcot District, Tamilnadu, INDIA.

W. GERSHON, B.A., Regional Secretary for India, German Leprosy Relief Association, 29c Gajapati Naidu Street, Madras, 600030, INDIA.

M. GOIHMAN-YAHR, M.D., Ph.D., Enfermedades De La Piel, Unidad Clinica "ESMARALDA," Av. Los Proceres, San Bernardino, Caracas, VENEZUELA.

S. D. GOKHALE, B.A., Dip. S.S.A., Assistant Secretary General, International Council on Social Welfare, Vice President, Indian Council of Social Welfare, 175 Dadabhai Naoroji Road, Bombay, 400001, INDIA.

R. S. GUINTO, M.D., Leonard Wood Memorial, Cebu Skin Clinic, Cebu City, 6401, PHILIPINES.

C. G. S. IYER, M.D., Director, Central Leprosy Teaching And Research Institute, Chingleput, 603001, Tamilnadu, INDIA.

R. R. JACOBSON, M.D., Ph.D., Chief of Medicine, U.S. Public Health Service Hospital, Carville, Louisiana, 70721, U.S.A.

C. K. JOB, M.D., F. C. PATH., Professor and Head of the Department of Pathology, Christian Medical College, Vellore, 632004, Tamilnadu, INDIA.

P. KAPOOR, M.B., B.S., D.P.H., Joint Director of Health Services (leprosy) Maharashtra, Pune—1, Maharashtra, INDIA.

A. B. A. KARAT, M.B., B.S., F.R.C.P., Consultant Physician, St. Catherine's Hospital, Birkenhead, Merseyside, U.K.

W. F. KIRCHHEIMER, M.D., Ph.D., Chief, Laboratory Research Branch, U.S. Public Health Service Hospital, Carville, Louisiana, 70721, U.S.A.

M. F. LECHAT, Professor of Epidemiology, Ecole De Sante Publique, Universite Catholique De Louvain, Bruxelles, BELGIUM.

M. S. MEHENDALE, M.A., B.Sc., B.T., Deputy Superintendent and Senior Research Officer, Dr. Bandorawalla Leprosy Hospital, Kondhawa, Pune, 411022, INDIA.

W. M. MEYERS, M. D., Ph.D., Chief, Microbiology Division, Department of Infectious & Parasitic Diseases, Armed Forces Institute of Pathology, Washington, D.C., U.S.A.

C. B. MISSON, M.D., Associate De Recherche, Ecole De Sante Publique, Universite Catholique De Louvain, Bruxelles, BELGIUM.

A. L. MURPHEY, B.S., Veterens Administration Hospital, San Antonio, Texas, 78284, U.S.A.

R. K. MUTATKAR, Ph.D., Head of the Department of Anthropology, University of Poona, Pune — 411007, Member-Secretary, Gandhi Memorial Leprosy Foundation, Wardha, INDIA.

S. K. NOORDEEN, M.B.,B.S., M.P.H., Deputy Director, Central Leprosy Teaching and Research Institute, Chingleput, 603001, Tamilnadu, INDIA.

D. D. PALANDE, M.S., Sacred Heart Hospital, Sakkottai, 612401, Tanjavur, Tamilnadu, INDIA.

S. R. PATTYN, Ph.D., Institut de Medicine Tropicale "Prince Leopold", B-2000 Antwerpen, BELGIUM.

J. C. PEDLEY, M.B., Ch.B., 33 Aldwick Crescent, Findon Valley, Worthington, Sussex, BN14 OAS, U.K.

G. RAMU, M.D., Deputy Director, Central JALMA Institute for Leprosy, Agra, 282001, INDIA.

D. S. RIDLEY, M.D., Consultant Pathologist, Hospital for Tropical Diseases, 4 St. Pancras Way, London, NW1 OPE, U.K.

O. ROJAS-ESPINOSA, Ph.D., Institute Politecnico Nacional, Escuela Nacional de Ciencias Biologicas, Mexico 17, D.F. MEXICO.

S. ROY CHAUDHURY, M.B., B.S., D.DERMAT., Assistant Director (Clinical), Central Leprosy Teaching and Research Institute, Chingleput, 603001, Tamilnadu, INDIA.

H, SANSARRICQ, M.D., Chief Medical Officer, Leprosy, Division of Communicable Diseases, World Health Organisation, Geneva, SWITZERLAND.

K. S. SEAL, Ph.D., Plymouth, England, U.K.

A. J. SELVAPANDIAN, M.S., F.A.C.S., F.I.C.S., Department of Orthopoedics, & Leprosy Reconstruction Surgery, Christian Medical College, Vellore, 632004, Tamilnadu, INDIA.

D. G. SMITH, Ph.D., Institute for Cancer Research, Philadelphia, Pennsylvania, U.S.A.

H. SRINIVASAN, M.B., F.R.C.S., Senior Orthopoedic Surgeon, Central Leprosy Teaching And Research Institute, Chingleput, 603001, Tamilnadu, INDIA.

G. P. TALWAR, D.Sc., Professor and Head of the Department of Biochemistry, All India Institute of Medical Sciences, Ansari Nagar, 110016, New Delhi, INDIA.

C. VELLUT, M.D., Hamerijckx Leprosy Centre, Polambakkam, 603309, Tamilnadu, INDIA.

G. P. WALSH, Ph.D., Armed Forces Institute of Pathology, Washington, D.C., U.S.A.

J. WALTER, M.D., Leprosy Unit, World Health Organization, Geneva, SWITZERLAND.

R. V. WARDEKAR, M.D., Chairman, Gandhi Memorial Leprosy Foundation, Wardha, 442103, Maharashtra, INDIA.

M. F. R. WATERS, M.B.Ch.B., M.R.C.P., Medical Research Council, National Institute for Medical Research, The Ridgeway, Mill Hill London, NW7 1AA, U.K.

P. VAN DEN WIJNGAERT, General Secretary, International Federation of Anti-Leprosy Associations (ILEP), 4, rue Saint-Geoffroy 80000 Amiens, FRANCE.

F. S. WITTENSTEIN, Ph.D., Institute for Cancer Research, Philadelphia, Pennsylvania, U.S.A.

A WINDOW ON LEPROSY

EDITOR'S NOTE

About this volume

It takes me back to the early sixties when I was taking a course entitled pathobiology 6, in essence leprology, at the school of Hygiene and Public Health of The Johns Hopkins University in Baltimore, U.S.A. It was almost wholly given by one Professor, and it almost appeared that there probably wasn't much there that called for more intensive team involvement. But, beyond our small world of Pathobiology 6 students, leprology started already to draw scientists of diverse disciplines. Shepard's footpad model had just appeared in the field with a big impact and immediately became a focal point of leprosy researchers around the world. And yet so many questions remained unanswered at the end of our course that quite a few of my fellow students at Hopkins wondered whether they got their 'money's worth'. I felt embarrassed because in the group I was somewhat identified with leprosy. More than a decade later, I can say without fear of contradiction that we do have answers to many of the questions asked by my fellow students in 1964-65. There has been a veritable explosion of knowledge and attempts are being made to utilise the fruits of research in the field with minimum delay. This has been made possible by a simultaneous appreciation of the great need to co-ordinate both the investigative and applied aspects of the new knowledge. The World Health Organisation (WHO) very rightly plays the pivotal role here. What is however lacking in all this is a free flow of the information and knowledge permeating through all levels of leprosy workers particularly in countries where leprosy is a big problem. Administrators, Medical Officers, para-medical and social workers, teachers and technicians who man the army of our fight against leprosy have little facility of finding out for themselves what new knowledge has accumulated and how. Even research workers in these countries have difficulty in collecting facts because of the limitations of library facilities readily available to them. In the All India Leprosy Workers' Conference at Baroda in April 1976, an experienced leprosy worker angrily reacted to the fact, according to his estimate, that scientists were miserly in response, or evasive to questions that the humble field worker had to constantly face in his day to day work, and that while a scientist could afford to be equivocal, the field worker had to face these questions with conviction or else he was ineffective. This is unfortunately true to a large extent. When we talked about bringing out a Volume to commemorate the Silver Jubilee of the Foundation, these thoughts were uppermost. Consequently, when I was asked to undertake editing of this volume, I readily agreed. My idea of a volume that will have articles from various laboratory and field investigators, dealing with specific issues, problems and topics in simple, narrative style, rather than subject-wise chapters, was endorsed by the committee members and I am most grateful to them for giving me a free hand in choosing the topics for the articles, the authors, and the format of the volume. The topics have been chosen to cater to all types of readers who are, or may be interested in the leprosy problem. As much as possible investigators identified with particular areas of research or activity had been approached and it is gratifying that most of them, inspite of their multifarious involvements and commitments, readily agreed to write the chapters asigned to them, conforming to the style, form and substance as detailed by the editor. Those that could not contribute had genuine difficulties and we appreciate that. Postal dislocation, i.e. non-receipt of letters in time at both ends posed some problems and was responsible for the absence of at least one vital chapter, the eye in leprosy. The authors were requested to use simple, easy to understand English without diluting the scientific contents. Those that have a natural gift of story-telling will have done very well, while there are admittedly articles dealing with topics that are indeed difficult of conveyance in simple style. There has been unavoidable repetition of facts in different articles. While these could have been rectified with a little effort, they have been left as they are for the simple reason that the overall impact of different authors'

differing ways of explanation of the same fact and statements should be more impressive and lasting.

Acknowledgements

Before concluding this note, I must have to acknowledge my debt of gratitude to all my friends, colleagues and seniors who have cooperated to make the volume what it has become. I am grateful to all the contributors for their ready response and for their extreme goodness in agreeing to design the articles according to editorial 'guidelines'. It is difficult to single out names for specific mention but I find it difficult avoiding altogether. Dr. Chapman Binford sent the whole chapter on leprosy from the book 'Pathology of Tropical and Rare diseases' from the press, being edited by him and Dr. Daniel H. Connors, and published by the Armed Forces Institute of Pathology, Washington, D.C., giving me the liberty of using any length of the text and illustrations from it. The article is so good, comprehensive and compact that I could not leave any portion out. I thank him and the co-author of the chapter Dr. Wayne M. Meyers, and the Armed Forces Institute of Pathology for the permission to reproduce this article, and another one on armadillos, with some little modification and addition. Mr. A. D. Askew the International General Secretary of The Leprosy Mission has helped us in two important areas, both involving finance. The Leprosy Mission has paid for the printing and air-shipping to Calcutta, of the colour and black & while illustrations of Dr. J. C. Pedley's article. It has also paid the return air passage for Dr. Browne's trip to India in connection with the release of the volume. Thanks are due to Dr. T F. Davey, Chairman, Editorial Board, Leprosy Review, and the Academic Press Inc, its publishers, for permission to reproduce these illustrations. Perhaps the most obliging of all the contributors has been Dr. Ridley ; he has done a good job of fulfilling the tall order of producing a 'tailor-made' article on the tricky business of classifying leprosy. Dr. Selvapandian, the orthopoedic surgeon that he is, obligingly accepted the humble assignment of dealing with physio-therapy. I am also grateful to Drs. C. G. Pandit, R. R. Diwakar, and R. V. Wardekar, and Baba Amte, members of the Gandhi Memorial Leprosy Foundation for their encouragement.

It would have been impossible to bring out the book in time without the generous help and good will of Mr. H. D. Singh, manager of the commercial printing department of the Statesman press, and his staff, particularly Mr. R. Sim, Mr. S. R. Das, and Mr. D. A. Ferris, chief of Statesman's process department that made scores of blocks, both in black and white and in colour in a matter of a few weeks time we could give them. Articles coming in as late as early January could be accommodated for their understanding attitude. No amount of thanksgiving is enough to express my gratitude to them.

Mr. Pradip Das, a lad of twenty who does my typing, has singlehanded done all the copying of the manuscripts often beyond office hours. Besides those named, there were many that helped in various ways and could not be mentioned individually for want of space. I thank them all.

January, 1978. B. R. CHATTERJEE

LEPROSY FIELD RESEARCH UNIT
THE LEPROSY MISSION, SIKRA HILLS,
JHALDA, WEST BENGAL,
723202, INDIA.

The volume has been ceremonially released from New Delhi at a function at the Mavlankar hall on the 30th of January, 1978, at 5-30 P.M. The meeting was presided over by Vice-President Sri B. D. Jatti who also released the book. Sri Morarji Desai, Prime Minister, was the chief guest. Dr. Stanley G. Browne, President, Royal Society of Tropical Medicine and Hygiene, London, and Secretary-Treasurer, International Leprosy Association, spoke on the Leprosy problem, Mahatma Gandhi's interest in leprosy and leprosy sufferers, and Indian scientists' contributions to the understanding of the disease.

सत्यमेव जयते

PRIME MINISTER

FOREWORD

Leprosy is a scourge of the human flesh which makes the individual afflicted by it not only suffer but also undergo the odium of an outcaste. Far from getting sympathy from his friends and relations; he is universally shunned; what is more, he has to bear the mortification of being an idle member of the community unable to play his part in the service of the country. The number of persons afflicted by leprosy is more than 3 million. It is therefore one of the main health problems of our country and needs a very scientific approach to its cure and to the dangers of infection. As a disease it has become a national problem and our country has never devoted to this problem the attention which it deserved except in recent years. We are now trying to control it through a National Leprosy Control Programme in which the Gandhi Memorial Leprosy Foundation has taken a pioneering interest. It was initially devised and put to field use by the Foundation and it forms one of the constituents of the Gandhi Smarak Nidhi programme which has as its theme the perpetuation of the memory of Mahatma Gandhi. Gandhiji was the apostle of the philosophy of "Daridranarayan" and for him there was no distinction of caste and creed, rich and poor and superior and inferior. It was this comprehensiveness of his mind, his deep compassion for the lowly and the suffering and his passion for healing the wounds from which humanity suffers which made him commit himself inter alia to the sufferers from leprosy. It was therefore fitting and appropriate that the ministration of relief to the leprosy sufferers should have occupied such an important place in the programme of the Gandhi Smarak Nidhi.

I am really very happy to see that the Foundation is commemorating its Silver Jubilee by bringing out a useful volume on the malady itself. The approach of the commemoration volume is commendably utilitarian. It brings to leprosy workers of all levels and shades of opinion the latest knowledge on various aspects of leprosy as a disease and the problem which it

poses to society. It will provide many a guideline for those who are engaged in ministering relief and I have no doubt that it will be a book of reference to all dedicated workers engaged in eradicating leprosy from the land.

However, the object underlying the production of this volume can only be achieved if all those who are engaged in research and service in leprosy can utilise it for carrying on well-planned and controlled scientific measures and studies in which they would use modern medical and technological methods and try to find out the good things which our Indian indigenous system of medicine has to offer. For some years it has been the habit to consider indigenous systems as archaic and of no value in modern times. After suffering from the ill effects of some modern drugs and medicines we have become wiser and have found utility and effectiveness in our indigenous systems. The realisation is growing that those systems could be widely used to advantage not only because they are cheap and locally available but also because they are effective and aim at eradication of disease and its causes rather than suppress the symptoms that they produce. The approach that has been made in collecting various contributions is motivated by this desire to utilise Indian indigenous systems to the greatest advantage without in any way running down modern system of medicine and cure.

I congratulate the Foundation for having brought out this volume and the Editor for having accomplished it so successfully and express the hope that the book would be widely circulated at home and abroad and would be appreciated by and prove useful to the readers.

New Delhi,
December 30, 1977.

Morarji Desai

(Morarji Desai)

GANDHI LOOKS AT LEPROSY

R. R. DIWAKAR

And he rushes to serve the patients at all costs and at all risks. If according to poet Shelly, 'our sweetest songs are those that tell of saddest thought,' our noblest actions are undoubtedly those that seek to remove all suffering from human life. If it is heroic to plunge into a rushing stream to save another life, it is the height of heroic patience to nurse back to healthy life a suffering patient, and a leprosy patient at that.

Buddha's insight declared that life was full of suffering and misery and his teaching of compassion moved Emperor Asoka to have hospitals even for ailing animals. It is said that Buddha preferred wiping the last tears of suffering humanity to the bliss of Nirvana. To treat all 'selves' as one's own, and be absorbed in their service (sarvabhoota-hite-ratah) is the philosophy and ethics of the Geeta. It is christian charity which inspires thousands to risk all to help all in distress. It is the sensitive heart and the responding soul of man that hungers to relieve others of all kinds of pain and suffering, be it of the body or mind. The essence of humanness lies in this sensitivity of our consciousness to the suffering of others.

Disease is as inseparable from life as death itself. Myriad have been the diseases, old and new, to which man has been subject from the beginning of his life on earth. Many of them have been quick in bringing about the end; several are painful and unbearable; some of them are prolonged and prefer to keep close company with their host till his death. There are diseases which are contagious, infectious, epidemic, endemic and so on. There are others which have their home in the human body itself and show themselves when times are favourable for them to burst out and attack mercilessly.

But there is no other human disease, which in addition to its intrinsic and inherent capacity to cause pain and suffering, has a number of attendant handicaps and associate man-made causes of alienation, ostracism, extreme disproportionate mental suffering, and reckless abandon as this disease of Leprosy in India and elsewhere. Even now, in this age of communications and wide-spread general knowledge, in this era of Welfare States and universal health care, in this heyday of science and technology as well as all-pervading humanism which bids to be a kind of future religion, leprosy is a malady which is looked upon by most as a curse, as incurable, as loathsome, as ugly, as dreaded, as a result of some deadly past sins, as highly infectious and so on. The social stigma which is attached to it by ignorant as well as educated people is still so persistent that even the nearest and the dearest are unwilling to entertain their own leprosy patients in the household. The leprosy patient is an untouchable and a social outcaste in the cruelest sense imaginable. It is this unjustifiable, irrational, primitive attitude towards this illness which prevents its being properly treated, and is responsible for its being called a scourge and what not. And yet we in India have to deal with the disease as well as with the obtuse attitude of people which is yet in evidence, though softening of late of that attitude on account of better and proper knowledge of the disease and its curability has started, though very slowly.

This fell disease often brings in its wake ugly deformities, especially of the extremities, of hands, of feet, of the nose, and the face. That is perhaps one of the main causes for the accumulated agelong prejudices. This disease has its own long and tortuous history. One need not think that this disease and the attitude towards it is peculiar to India. I may quote here from an excellent article by Alec Walker, which recently appeared in the Sunday Edition of 'Deccan Herald' (4.4.1977) of Bangalore.

'No one knows the origins of leprosy which is as old as the world itself. Egyptian

accounts tell of a disease resembling leprosy as early as 4600 B. C. In the Angkor sanctuaries in Cambodia there is the statue of the *Leper King whom some authorities think is King Yasovarman I, founder of Angkor and builder of Phnom Bakheng, who is said to have died a leper.

Chow Ta-kuan, a chinese traveller of the 13th century speaking of lepers in this place says that it is a disease people in the area are accustomed to and 'though they live and eat with them, people do not catch the illness.'

There has always been deep-seated prejudices and fears that leprosy represents a 'divine curse'. Among Hindus this affliction suffered in this life is a form of punishment for misdeeds in a previous incarnation. Among Muslims it is believed that leprosy is imposed by the will of Allah to be borne stoically. It also provides the faithful to gain heavenly credit by giving alms to them. In biblical times, lepers were treated as outcasts and people fled from them. They were segregated from the rest of the inhabitants and pronounced unclean. It was considered not only a disease but an affliction placed upon many by God because of his sins.

Such beliefs and prejudices still persist inculcating attitudes of fatalistic acceptance and resignation on the part of the afflicted and his family. They have not been properly taught and do not know that leprosy is curable, it is not hereditary, it is preventable, and that it is not the result of any curse. It is caused by germs like that of tuberculosis. Early treatment can prevent deformities and most deformities can be corrected by surgery. It is not a hopeless and highly infectious disease.'

It was but natural and human for Gandhi to have been drawn to this problem of leprosy in India. In view of our overwhelming regard for the Father of the Nation, and in view of the deep debt that India owes to him for inspiring millions to sacrifice their all for wresting independence from the clutches of a mighty foreign power through unique non-violent means, we are likely to forget or make light of the other great contributions he has made for the uplift of the masses and for the relief of the lowliest and the last in our society. He was not only a seeker of truth in all its purity, but a votary of Truth and one who would spare nothing to establish the truth, once he found it and was convinced of it. He was a humanist par excellence and his interest were as comprehensive as human life itself, his concern was as deep for its betterment as his vision was wide as the whole of humanity. How then could this disease with its vicious ramifications and manifold sufferings escape his sensitive soul and vigilant eyes.

As early as when he was thirteen he came in contact with one Ladha Maharaj who had cured himself of leprosy as much by medication as by his faith in Ramanama, his devotion to God. He used to read the scriptures for Gandhi's ailing father while the boy looked on and listened. So, Gandhi's knowledge of leprosy as well as of the importance of devotion to God were almost simultaneous. Both sank deep in the young mind of Gandhi to mature at leisure and flower most abundantly for the multiple benefit of humanity.

Gandhi looked upon leprosy as a bad disease no doubt. He said, the word had a bad odour. But some times, he abhorred 'moral lepers' in society more, and attributed the ills from which human beings suffer to the several sins committed by man. His feeling for those suffering from leprosy was not the common & customary sympathy which all of us usually have for all sufferers. It had its roots far deeper in his heart which could readily respond to the slightest ache of sentient beings. It was not merely the suffering, the ugly sores & the deformities of leprosy patients which moved him to action but it was more the inhuman and disgraceful way the other humans treated their brethren who were victims of a crippling disease for no fault of theirs. This double curse from which the victims suffered that stung him deeply. It made him rebuke his coworkers in Durban when they remonstrated him not to waste his time with a bunch of leprosy sufferers whom he met under a tree. Gandhiji would say, we Indians here in South Africa are ourselves out-castes, and we are treating these miserable brethren of ours as outcasts among outcasts. What an irony? Do they not deserve a few kind & consoling words from us if not any thing more?

On another occasion, while in Madras during his earliest tour of India, when Gandhiji heard of a senior Founder-Member of the Indian National Congress suffering from leprosy, he simply rushed to his bedside, and while making enquiries wiped his wounds with the ends of his own garment. The Honour-

*The use of the word 'leper' has been officially banned by the Govt. of India—Ed.

able Shriniwas Shastri who was with him at the time was stunned; he has described this incident as follows:

'He (Gandhiji) knows no fear and Shrinks from nothing which he advises others to do. In fact, his love of suffering and hardships as a means of spiritual progress is almost morbid. His compassion and tenderness are infinite like the ocean—to use an Eastern simile. The present writer stood by as he wiped the sores of a leper with the ends of his own garments.'

Neither reason nor logic, much less commonsense or caution can explain the abandon with which Gandhiji rushed to relieve the suffering not only of leprosy patients but the suffering of all humanity, often at the risk of his own life. His sympathy which had already matured into empathy had its roots in the intuitive perception of oneness of all; sense of identity, love, compassion' fellow-feeling, greater concern for others than for self, urge to serve all, are but corollaries of the great principle Gandhiji enunciated in the simple phrase 'All life is one'.

Gandhi's compassion and fellow feeling overrode all fears of infection and such other considerations. Readers may have a full idea of Gandhi's commitment in the matter of leprosy if they read a small book 'Gandhi Looks at Leprosy' written by Shri M. S. Mehendale and brought out by Bharatiya Vidya Bhavan, Bombay-7, on behalf of the Gandhi Memorial Leprosy Foundation, Wardha, 442103. In 1945 Gandhi included leprosy work as one of the many items of Constructive Program which was accepted by the Indian National Congress. He thus gave leprosy work a place and a status in the national reconstruction of India.

Though leprosy has been an ancient disease affecting the whole of mankind, it is the modern scientific age which has been able to probe into its etiology and many scientists are at present desperately trying to find an effective remedy. It was only as recently as 1949 that the sulfone drug DDS has been found to be effective if used in early stages and continued to be used for long. It can arrest the disease and also prevent deformities. It is now possible to detect and mark off lepromatous cases which are infectious as different from non-lepromatous which are not infectious. But the final remedy can be said to have been found only when the rod-shaped leprosy bacillus (Mycobacterium leprae) can be cultured outside the human body and an anti-leprosy vaccine manufactured on a large scale. It may also be possible to eradicate the disease if some kind of immunity is established as a result of the effort of immunologists who are working at it. Though it is about hundred and four years that the bacillus has been isolated and found to be the cause of leprosy by Dr. Hansen of Norway, it has not been possible to develop a vaccine, or to induce immunity, try how they might.

In the meanwhile however, we now know that the discovery of the patients, administering the available drug at the earliest, and persistent use of it effectively cures the patients, prevents deformities and stops dehabilitation of the sufferers. This is no small gain. Surgery in the case of Deformities also has advanced a great deal; care of the eyes of leprosy patients can prevent blindness, thus adding a new dimension to the lives of those who have been suffering. Both these feats of surgery and eye care have been in evidence and the recipients of this year of the Damien-Dutton Award, Dr. Paul Brand and his devoted wife Dr. (Mrs.) Brand, have proved that these can be practical achievements and not mere propositions. If the great Martyr Father Damien and Brother Joseph Dutton have proved that living in the midst of leprosy patients and serving them at far off Molokai in Hawaii Islands is worthy of one's life's highest objective, Drs. Brands, husband and wife have proved that skills in surgery and care of eyes can save many a patient from the misery of being dependent cripples and blind helpless creatures.

While this in brief is the position of the disease, it is rather disconcerting to see that the prejudices against leprosy patients and the social shunning attitude towards them are still not very much on the decline. Private practitioners, on account of the public attitude are still hesitant to treat them like any other ordinary patients. Illiteracy, superstition, ignorance, the doctrine of Karma and Kismat are still operating on the minds of millions to the detriment of the unfortunate sufferers who are the flesh of our flesh and the blood of our blood.

We in India are now 600 million and still on the increase. It is calculated that we have about thirty two lacs (about 25% of the world's leprosy population) who are suffering from leprosy of one kind or the other. All these are patients at one stage of the disease

or the other. We see leprous beggars on streets but more are seen congregating at fairs, temples and other places of public worship. Most of them are 'burnt out' cases and are mostly non-infectious. There are lacs of others who are suffering silently and are on the way to dehabilitation when they will join the ranks of the helpless wanderers. But a large number of them are just affected and need quick detection and instant treatment which today is effective. It is obvious that the formation of segregated 'leper' colonies of the old type is not only impracticable and impossible for such a vast number, but in principle, is no real remedy as it perpetuates the deep-rooted prejudices and social alienation and mental suffering. It is necessary therefore to tackle the problem as we tackle other diseases since an effective remedy, the sulfone drug for cure has been found. After long research and experimentation, the Gandhi Memorial Leprosy Foundation of Wardha, has been able to go about it by intensive survey, locating the patients, giving them presistent treatment and thus curing them and preventing deformities and dehabilitation. Rehabilitation of cured patients must mean the absorption of the cured patients with the society in general as they are as innocent as others. The government has accepted this methodology no doubt. But its application on a national scale and in a persistent manner throughout India, and especially in areas which are sensitive, is an immediate necessity. It has to be a national planning program till such time as immunity becomes a fact and/or an anti-leprosy vaccine is available on the required scale.

Where does all this lead us to? Gandhi has led the way here as in many other respects. The heart and the feeling for the sufferer must take precedence and the lead. The quality of fearlessness will supply the required courage to tackle the problem boldly. Are we, who boast of our spirital culture to continue to be callous about the sufferings of our 32,00,000 kith and kin? This is a national problem and every Indian citizen worth the name has to be aware of his responsibility to wipe out this cause of unwarranted suffering and see that every sufferer feels free to be treated openly and to the end. Every facility has to be given to every leprosy patient as to any other patient. Every doctor has to educate people as to the real nature of the disease and treat leprosy patients as he treats other patients. Every leprosy worker should be honoured as a missionary in a great cause. In the meanwhile, every school and college, every media of communication should be used for educating the people of their duty in dealing with this agelong disease, which is no longer an incurable curse nor an easy infection. Every sufferer deserves sympathy and treatment and care. It is the duty of all to make the patients of leprosy feel that they are like any other patients, without any stigma attached to the disease. Such sympathy solves more than half the problem of leprosy. Let us all work on in the hope of a new day which is sure to dawn when immunity would be secured and/or vaccine will be available, both of which will mean new life to millions. Let Faith in the Moral Order of the world, hope in the great future of humanity, and charity towards our fellowmen be our guides in this as in other matters.

CHAIRMAN'S NOTE

R V WARDEKAR

Gandhi Memorial Leprosy Foundation completed 25 years of its existence in 1976. But due to certain difficulties it was not possible to observe its Silver Jubilee at that time. It has now been decided to do so from 2nd October 1977 to 30th January 1978. This Commemmoration Volume is a part of the Silver Jubilee programmes. As the Chairman of the organization it is perhaps expected of me to write a few words about us and make some general comments. I will be necessarily brief, as I understand from the editor, Dr. B. R. Chatterjee that the volume is going to be 'stuffed' with readable material of more tangible interest.

After introduction of the Sulphones in India, this institution was the first to start centres to study whether it was possible to control leprosy by *Survey*, *Education* and *Treatment* (SET method), using Sulphones. Referring to the method adopted by this institution for leprosy control, two years later Muir (Lep. in India, 1953 : 21 : 231-234) wrote—'Attempts were made to start work along those lines in India more than 25 years ago, but met with very limited success at that time. Recently Gandhi Memorial Leprosy Foundation, a branch of the Gandhi Smarak Nidhi (Gandhi Memorial Fund) has worked on a scheme for setting up sample centres of this nature in all of the Indian states, and for training doctors and social workers'. Muir was obviously referring to propaganda, treatment and survey (PTS method) suggested by him years ago when Hydnocarpus oil was the drug for treatment of leprosy, and he also admitted that it 'met with very limited success at that time.' It may thus be said that without its knowledge this institution had in a sense revived the almost forgotten PTS method of Muir's under the name, SET method. Posterity will judge if this institution has made any contribution towards control of leprosy in India, and elsewhere. All I can say is that we worked hard and with some purpose and direction. The *Survey, Education* and *Treatment* (SET) pattern evolved and field-tested by us continues to be the pattern of work in the country, more or less unchanged. However, with development of new knowledge on the diseased host, the parasite, and the epidemiology of the disease, discovery of newer drugs and particularly the knowledge and appreciation of the fact of drug resistance and its danger, the fixed pattern of work may need to be modified. While the dispensation of treatment has to continue to be clinic based, exigencies of the newer developments undoubtedly calls for experimentation through field trials to develop easier-to-adminster, safer, more effective and cheaper combination of drugs.

It gives me satisfaction to see the increasing awareness of the value of health education that we have been advocating and demonstrating through a number of health education units in the country, and a special leprosy health education training course at Wardha. A nascent debate is on whether health education alone is enough to bring all cases voluntarily to the clinic for treatment, and can do away with the time consuming total village surveys that are seldom done properly, and on schedule. Similarly, it is being debated whether early, single patch lesions should be treated or rather be kept under observation, thereby reducing the load on the clinic, and anxiety of the patient, his family and the community. These are some of the areas that need to be investigated thoroughly in well defined populations over a course of several years. I am happy to say that the Foundation has undertaken field investigations to explore some of these areas outlined above in a new experimental control unit at Balarampur in the Purulia district of West Bengal.

Lastly, I feel impelled to dwell a little bit on the subject of integration. As we all know the Government of India has taken the decision to abolish all vertical health programmes, including leprosy, and bring everything within

an integrated set up. There is no doubt that this is the ideal arrangement in view of the social stigma attached to the disease that keeps patients away from the leprosy treatment centres for fear of identification. We plan vertical programmes for particular health problems in order to bring down the intensity of the problem to a manageable level whereby it can be tackled as any other community disease through the general health care and delivery system i.e., the primary health centres. There are knowledgeable writings in other sections of this volume that deal with the current state of the leprosy problem in the country. One need not re-emphasize the fact that we fight the leprosy problem on two fronts, the medical, and the social. This unique situation is peculiar to leprosy. I have a strong conviction that treatment of leprosy in an integrated set up may be neglected unless there is adequate social acceptance of leprosy. I do not want to go into the debate on whether the control programme has failed or succeeded. All I can say is that, it has not been implemented the way it should have been, and has been largely neglected by the components of the administration that matters, viz, health and finance. Keeping all these in view, and the newly emerging knowledge on the disease and the parasite outlined earlier that calls for newer field trials and re-orientation of the pattern of work, I feel that integration at this stage is premature, and may cause more harm than good.

Dr. B. R. Chatterjee sportingly accepted the Editorial responsibility. Though the time at his disposal was short, he managed to produce the volume that contains a large number of articles of contemporary interest from many of the leading scientists and field workers in leprosy in India and abroad. On behalf of Gandhi Memorial Leprosy Foundation and myself I thank Dr. Chatterjee and all the contributors for their willing cooperation.

GANDHI MEMORIAL LEPROSY FOUNDATION

On an invitation to open a leprosy hospital Gandhiji wrote, 'Get someone else to open it ; opening a hospital is not a big matter, but I shall come to close it.'

Gandhiji tried to remove the social stigma attached to leprosy in many ways, fearlessly handling the patients, dressing their wounds and otherwise looking after them, and educating the public. How correct was his advice when he said, 'There is another type of medical relief which is a boon. It is given by those who know the nature of the disease, who will tell the patients why they have their particular complaints and will also tell them how to avoid them. Such discriminating relief is an education in hygiene, teaching the people how to observe claeanliness and to gain health'. It was not surprising, therefore, that in view of Gandhiji's life-long interest in leprosy work and the need to complete the work in a fitting manner, the Gandhi Smarak Nidhi decided to take up leprosy work as one of the appropriate memorials to the Father of the Nation to be set-up in India.

I. Birth of Gandhi Memorial Leprosy Foundation

The Gandhi Memorial Trust, also known as the Gandhi Smarak Nidhi, was formed on 17th February 1949. In response to a proposal from Shri Devdas Gandhi to take up leprosy work as one of the activities of the Nidhi, it was resolved by the trustees that help from the Nidhi should be given to both leprosy and tuberculosis work, and Rajkumari Amrit Kaur, (later Union Health Minister) was deputed to submit concrete plans for work in both these spheres. The Gandhi Smarak Nidhi considered the report of the Committee under the Chairmanship of Rajkumariji on 26th February 1950, and in November 1950, the Executive Committee of the Nidhi with Sardar Patel in the chair appointed a Leprosy Advisory Board of 15 members who were to prepare a plan for leprosy work of the Nidhi. This was done on the recommendation of a sub-committee which met on 28th and 29th April 1950 where Dr. Pandit and Dr. Raja were specially invited.

About two years before the formation of the Leprosy Advisory Board, there was a very significant development in respect of treatment of leprosy. This was the introduction of parent sulphone as a potent anti-leprosy drug. This new development coupled with Gandhiji's outlook on leprosy described before, his emphasis on health education and prevention, and the size of the leprosy problem were the main considerations which prompted the Leprosy Advisory Board to make the following recommendations :

1. The aim of the Leprosy work under the Nidhi (or Trust) should be the control and eradication of leprosy in India and not mere relief operations. The Nidhi should encourage and undertake pilot projects wherever conditions were suitable. The underlying principle of these pilot projects should be to trace and treat all cases and to keep all contacts of leprosy cases under careful observations.
2. It should be realised that there were several questions which needed to be answered before an effective scheme of control on a large scale could be worked out, as for instance the value of various types of segregation, the mode of spread of infection, the relative value of different treatments and modes of rehabilitation. Investigations aimed at providing answers to such questions should be encouraged.
3. While the pilot projects and investigations would be working and evolving an effective scheme of control and eradication of the disease, the Nidhi should also take up the work of training workers, lay and medical, for the service of leprosy patients. These should include among others, personnel for scientific investigations.
4. The Nidhi should become an effective agency for applying new knowledge and for developing field work. It should also become an effective agency for educating the public and finding out effective means

of rehabilitating disease arrested cases of leprosy.

The Board made many other recommendations and also adopted a constitution. Since it was not possible for the Leprosy Advisory Board to meet frequently it suggested appointment of a small Executive Committee for supervision and execution of the schemes.

Accordingly, the Gandhi Smarak Nidhi formed a Kushta Nivarak Salahakar Samiti on 6th December 1951. The following were its members.

Dr. Jivraj N. Mehta	—	*Chairman*
Dr. Sushila Nayar	—	*Secretary*
Dr. Dharmendra	—	*Member*
Dr. V. R. Khanolkar	—	,,
Dr. C. G. Pandit	—	,,
Shri Manohar Diwan	—	,,
Prof. T. N. Jagadisan	—	,,

The Samiti was also to act as a central organisation charged with the duty of coordination of all leprosy work carried out in the country by official and non-official agencies. Guided by the recommendations and resolutions of the Leprosy Advisory Board, the Samiti examined the various schemes for (a) Training and Research, (b) Control and (c) Relief. Some of the schemes in the above categories including leprosy control in Wardha District, were started. The most important contribution was, however, the study of the extent of the leprosy problem in India.

The magnitude of the work of Kushta Nivarak Salahakar Samiti necessitated services of a full time Secretary. As Dr. Sushila Nayar was engaged in many other activities, Dr. R. V. Wardekar was appointed as Secretary from 30th January 1952 and the Gandhi Smarak Nidhi decided to reorganise the Samiti. The name of the Kushta Nivarak Samiti was changed to Gandhi Memorial Leprosy Foundation in August 1952 and ratified by the Nidhi in April 1953. In December 1953 the Leprosy Advisory Board was abolished and the Foundation was working as the leprosy section of the Nidhi.

In 1961, the Gandhi Smarak Nidhi approved a scheme for decentralisation of its work and as a result the Gandhi Memorial Leprosy Foundation became an autonomous body with independent registration. From March 1970, the Leprosy Fund of the Gandhi Smarak Nidhi has been earmarked for Gandhi Memorial Leprosy Foundation.

II. The magnitude of the leprosy problem in India in 1951

In 1951, it was estimated that India had about 15,00,000 leprosy patients out of whom over 3,00,000 were infectious. It was found that only 5 out of 100 infectious patients were isolated in the colonies, and only 7 out of 100 non-infectious patients were taking treatment. The routine treatment in those days used to be hydnocarpus oil injection. The sulphones (DDS) were recently introduced. The only recommended way of control was isolation of all infectious cases in leprosy colonies. There were about 100 leprosy colonies in India with total accommodation for about 15,000 patients. Thus, even to isolate all the infectious patients at the prevailing rates it would have involved a non-recurring expenditure of Rs. 45,00,00,000 and then involved a recurring expenditure of 15,00,00,000 annually. Institutional isolation or segregation was therefore considered impracticable in the control of leprosy. Some leprosy colonies were no doubt necessary to provide for the homeless, grossly deformed and otherwise totally disabled patients and indeed other agencies were maintaining such colonies.

There were over 1,000 leprosy clinics in India in 1951, but these were purely treatment centres and not much control work was done there. Only treating the known patients would never control leprosy. Adequate treatment was certainly essential, but it was necessary to make this a part of control measures which should include finding out each and every patient, treatment of all the cases of leprosy, both early and late, keeping of a close observation on close contacts, educating the people in leprosy etc,.

There was also the problem of the beggar leprosy patients, and as it is even today, this problem was equated with that of leprosy itself.

Misconceptions, wrong information and ignorance about leprosy were common all over the country, both among the illiterates and educated. Even the medical profession was not free from that. There was almost total ignorance about the scientific facts about leprosy. Since active co-operation of the people was essential in all control and eradication programmes, it was considered that

health education of all types of people should receive a high priority.

The discovery of the sulphone remedies called for a reorientation of policies in the matter of leprosy control. It was now possible to contemplate that most of the infectious patients of leprosy could be rendered relatively non-infectious within a period of about 2 years. The new treatment of leprosy was still in the experimental stage, but the results all over the world were so encouraging that Dr. C. G. Pandit was the first to suggest the use of the sulphone drugs in prevention (prophylaxis) and control programme for leprosy on an experimental basis. He emphasised the need to bridge the lag between knowledge and its practical application in the field. It was essential to collect reliable and dependable data for the success of any control programme in leprosy.

To deal with a problem of this size large number of workers genuinely interested in leprosy work would be needed and arrangements made for their training. It was however not easy to get such workers. Moreover there were no adequate arrangements for their training. These were the circumstances when the work was to be initiated by the Foundation.

III. Formulation of basic policy of Gandhi Memorial Leprosy Foundation

Though the ideal of the Gandhi Memorial Leprosy Foundation was to eradicate leprosy from India, it was also realised that scientifically it was unattainable in the near future. It was decided therefore to have as an immediate objective a high level of control so that leprosy ceased to be both a social and public health problem.

It was decided to ascertain whether planned use of DDS in a population could control leprosy. Since medical men were not available and since such a programme, to be successful, would require a large number of trained workers, it was decided to find out the usefulness of paramedical workers for some aspects of control work.

In view of the above the Foundation adopted the following policy for its future work :

1. To organise experimental field projects to find out practical solutions to the different aspects of the problem of leprosy control.
2. To undertake basic field studies.
3. To take all necessary steps to apply the know-how worked out by the Foundation in its experimental studies, for a nationwide control programme.

Accordingly, the following programmes were devised and implemented :

1. Ten Leprosy Control Units were established. The first Unit was started in 1951 at Sewagram near Wardha and 9 more were started in different parts of the country, viz. Chilkalapalli, Mararikulam, Parlakimedi, Kundahit, Sriniketan, Gorakhpur, Jamner, Bardoli and T. Narsipur. The last Unit at T. Narsipur was set up in 1955. Each Unit covered a population of about 25,000 with an estimated prevalence of 30 per 1,000. It is through this work that the concept of SET Units (Survey, Education and Treatment) was evolved and was adopted all over the country by the Government of India.

2. Eight Health Education Units were established in urban areas in different parts of India to stimulate the local agencies and authorities to educate the people and study the effect such education had in case detection, encouragement in suspecting leprosy and consulting a doctor, inducement to take treatment, removal of social stigma, etc. This programme was also designed to evolve a practical method for Urban Leprosy Control Work, and to encourage the local authorities and the people to establish units for Urban Leprosy Work.

A lot of health education material was prepared. This included films, coloured transparencies, posters, charts, leaflets, books etc.

3. Programmes for adequate training of doctors and medical students were initiated and encouraged so as to ensure correct and factual knowledge, and development of correct attitude towards leprosy. Teaching aids were developed for this purpose.

4. Training centres were established for preparing the paramedical workers and officers who would effectively undertake work of leprosy control, both in the rural and urban areas, and participate in the projects.

5. In order to ensure nationwide implementation of the research findings for control of leprosy, the Foundation involved itself in the planning of the National Health

programmes with Central and State Governments, and the planning commission. This resulted in the acceptance of control and S.E.T. Units as a National Policy.

6. In spite of the early success of the control units, there were certain problems which required detailed and prolonged studies. The Foundation engaged itself, with grants from the Indian Council of Medical Research, in a large scale mass chemoprophylaxis project to study the effect of DDS in preventing leprosy in persons below the age of 25 years.

THE RESULTS OF DIFFERENT ACTIVITIES

The Leprosy Control Units

In the four leprosy control units, there was a decline in prevalence rate ranging from 33% to 72% and also a decline in the quantum of infection ranging from 36% to 71.9%. Regarding frequency of occurrence of deformities, Dr. Wardekar has reported that out of 1449 patients discovered in the initial survey in the areas of control units 26.4% had deformities but among the 2285 patients discovered in the subsequent follow-up survey in the same areas only 8.4% had deformities. This showed the usefulness of surveys in discovering patients in early stages.

Thus out of 3734 total cases discovered in the units, 3159 had no deformities at the time of detection. Of these patients free from deformities at the time of detection, treated with sulphone and followed for 2 to 13 years, 5.4% developed deformities. Among patients detected in initial surveys in virgin areas (where the patients had not received any treatment till the Foundation's work was started) 26.4% had deformities.

In the early years of work, there was appreciable reduction in the number of new cases (incidence) from year to year, but after reaching a certain level after about 10 years of work, there seemed to be no further decline.

It appeared that decline of leprosy has reached a limit in the Control Units of the Foundation. Reasons for this new ecological balance were not known, but limitations of DDS itself could be an important factor. It appeared that leprosy could not be eradicated with chemotherapy alone.

It was doubtful whether the control units of the Foundation will further help in throwing any new light on the natural history of leprosy, unless drastic changes were made in the working so as to find out answers to questions such as, what could be done to achieve a continuous reduction in incidence, what factor or factors were responsible for the occurrence of new cases even when the quantum of infection in the community was low, etc.

Health Education Unit

Health Education Units were established to stimulate the municipal and other agencies to take up urban leprosy work in their respective areas. The work was to be based on the same major activities as in rural areas, viz. case-detection and treatment. Health Education was to be used for case detection and for treatment, the services of the usual medical facilities such as general practitioners, government and other dispensaries etc. were to be involved.

After about three years of work, it was noticed that no agency was prepared to start health education units on their own, mostly because of limited financial resources.

The foundation then tried to organise refresher courses mostly for general medical practitioners but the progress was very slow.

Another group which appeared potentially significant because of its large-scale contact with the community in the course of the usual daily function was the teachers. As a practical consideration, teachers under training in colleges of education were selected. The impact of this education on the school-children has not been evaluated.

A lot of materials and audio-visual aids have been produced to educate the public, especially urban people.

Work related to Rehabilitation

Through its work the Foundation realised that true rehabilitation of leprosy patients was their return to their family and own society where they lived, and not to settle them separately elsewhere.

Referral Hospital at Wardha

This hospital was started to provide specialists consultation for diagnosis and investigation of leprosy patients, for treatment of complication, for reconstructive surgery and for demonstration of how referral centres should be established at district level or

regional level. It has also been utilised for training of Medical Officers in leprosy, and paramedical workers and supervisors. It has served its purpose well.

Chemoprophylaxis Project

This was one of the basic scientific studies the Foundation undertook to find out new measures for the control of leprosy.

Initial expectations in this project were satisfied only partially. Chemoprophylaxis resulted in significant reduction in the incidence of leprosy, especially among children. But, as in the leprosy control units, soon a limit was reached and there was failure to arrest transmission of infection completely.

Training Programmes :

From the very beginning of the contral work in the country, training of leprosy workers of various categories have been one of the main activities of the Foundation. Until the time of preparation of this report, 957 paramedical workers in 40 batches, 88 doctors in 20 batches and 166 health educators in 19 batches have been trained. The trainees have come from all the states of the Union, and from both government and private institutions.

NEWER ACTIVITIES

As already mentioned earlier in this report, in the old control unit areas the endemicity has more or less come to a point where further experimentation or pilot trials on newer lines may not yield results. While at the same time, there is a great need for new field trials for devising control methods in the light of recent developments, newer knowledges and ideas. Multiple drug regimen to prevent development of sulphone resistance, quicker attainment of bacteriological negativity and interruption of transmission seems to be of the highest priority. Similarly, to establish unequivocally the value of health education as a substitute for expensive mass surveys, well planned field studies are necessary. A new control unit has been started in West Bengal in Balarampur of Purulia District with a population of 200,000 to experiment along these lines. Besides the planned studies outlined above, one other main point of reference is, whether the leprosy problem can be brought down to manageable proportions within a reasonable period of time and within the scope of our existing state of knowledge. Therefore the inputs in terms of manpower and latest know-how is going to be higher than the prescribed norm for a standard control unit.

Some of the older control units where the prevalence rate has come down substantially, are in the process of being phased out or transferred to the government control units. It has been decided to continue the other units that still have a high enough prevalence & incidence rates for further experimentation with alternative drugs & combinations, and possible immuno-potentiation therapy.

Lastly, from whatever has been learnt, from our own experiences and that of others', on the value of health education, it is going to be the spearhead of the foundations activities over the coming years. The foundation would like very much to have one health-education bureau for each of the states of the Union to serve as a liaison office between itself, the state government and other voluntary agencies, to continuously carry on health education and leprosy orientation of the population, the medical profession and health personnel, and organise and participate in seminars, exhibitions, lectures and other such activities that have the maximal community reach, to remove the fear of leprosy in the community, make people knowledgeable about basic facts of leprosy and encourage the medical profession, both general & specialised, to take up leprosy treatment as a routine. Naturally, such an organization has to be well staffed with qualified and competent workers, particularly in states that are leprosy endemic. Financial constraints, and the problem of recruiting and holding of suitable men for such positions has been the main difficulties in the way.

(Based on the Gandhi Memorial Leprosy Foundation's Assessment subcommittee report, "In Retrospect and Prospect". *Editor.*)

SOCIAL ASPECTS OF LEPROSY

R. K. MUTATKAR

Leprosy has always been abhorred in human society. The social stigma attached to leprosy is universal in all societies, unlike the stigma attached to racial and untouchable groups. The stigma of leprosy creates a brotherhood of leprosy patients distinct from such social groups as family, class or caste. As in other social groups, in-groups based on the various stages of the disease are formed among the leprosy brotherhood also. The patients with ulcers feel closer affinity for each other than those with nodules or patches. There is no other disease the stigma of which unties an individual from socially recognised groups and binds him with stigmatised individuals suffering from the same disease. One wonders whether this group formation is comparable to a criminal gang, a group of deviants. It appears, however, that the criminals have a status in the society and they evoke sympathy with a view to be reformed. The leprosy patients do not evoke sympathy in society but are rejected by one and all. The crisis created by social rejection and stigma creates a separate group of leprosy patients. Unfortunately the law of the land takes cognizance of such groups in the same spirit as that dealing with social deviants. The involvement of legislation in a chronic disease like leprosy further complicates the social problems connected with the disease.

The social system can be understood in terms of continuing, structural relationships amongst individuals and groups. The statuses such as those of father, mother, son, daughter, teacher, priest etc., are universal and are socially defined. The structural relationships amongst these statuses explain the structure and functions of various social groups. Family is a nuclear group in the society, the relationships of the members being personal, spontaneous, emotional and irreplaceable. Physical intimacy is prescribed by the society among these relationships. Lack of intimacy is considered abnormal and may lead to divorce between spouses. The law supports socially approved intimacy.

In contrast to such a situation as seen in a family, touch is proscribed between caste groups occupying the higher and lower positions in caste hiearchy. In India, of the total population of about 600 million, about 80 million belong to the outcaste groups who are known as untouchables or as scheduled castes as per the constitutional provisions. These untouchables suffer from stigma and as such suffer from civic, social, economic and religious disabilities. The law is helping them to get over this stigma by removing the disabilities and by prescribing certain privileges to bring them to the level of other people in the shortest possible period. The intimacy between the 'blacks' and the 'whites' is also proscribed in most of the socio-political systems. It is not uncommon, even now, for a Negro raping a white woman, to be awarded punishment for 200 years.

The untouchables and Negroes are born into their respective groups and are ascribed the stigmatised status at birth. A leprosy patient is driven to a stigmatised status at any period in his life after living a richer life in his social group in which he is born. In the life of a leprosy patient there is a sudden change in his status irrespective of whether he belongs to a particular class, caste or religious group. An untouchable leprosy patient is equally rejected by his group as a Brahmin patient would be by the Brahmins. The disease of leprosy therefore makes a patient more disprivileged than the socially disprivileged.

The untouchables and the blacks continue to get their bio-psychic needs of affection and belongingness satisfied in their own families and social groups. A leprosy patient rejected by the society is however deprived of satisfaction of his bio-psychic needs.

A human being lives in society as a person, i.e. as an individual occupying certain position, status in a social system. A man lives as a son, father, husband, brother and roductive member of the society which also holds true for a woman. Each person performs certain roles in a society commensurate with his status and for which he is trained. A person derives a sense of usefulness and fulfilment in society. Sometimes, for a limited period, when a person is unwell, he is given the status of a patient by the society. He is then governed by the doctor-patient relationship, perform the sick role which is accepted in his family and at his place of work.

A leprosy patient however becomes a no-person in the society. Even many members of the medical profession are reticent to accord him the status of a patient as is given to persons suffering from more 'respectable' diseases. A leprosy patient ceases to hold his ascribed statuses of fatherhood, husbandhood etc, as also the achieved statuses at the place of his work. The status accorded to him of a leprosy patient is the status of social death, a status which has no roles in society to perform.

A Hindu Sanyasi is also a no-person in the society. He is considered formless and having mastered his senses is considered superior to humanised deities in the temples who are showered with the choicest of human luxuries. He is bestowed with powers to bless these deities. A sanyasi does not belong to family, caste or class like a leprosy patient, but unlike him, rejectes membership of these groups of his own choice by embracing sanyas. He can still function as a useful member of the society by accepting and training disciples. A Sanyasi is respected in the society and is worshipped like God. He is considered fittest to attain 'moksha'. His belongings are considered sacred and they may be preserved by his disciples as sacred objects after his death. Death rites are performed on a person becoming a sanyasi. They are also sometimes performed for a person afflicted with leprosy. The death rites symbolise the cancellation of membership of the society. Thus, both a sanyasi and a leprosy patient lose their social identities or membership of social groups for different reasons and with different results. However, a sanyasi is closest to 'Moksha' while a leprosy patient is at the lowest rung of the spiritual ladder, being identified in the society as sin incarnate. The disease of leprosy and the social stigma attached to it brings about this contrast in the category of two no-persons in the society.

The blacks, the poor and the untouchables are not no-persons in the society. They may be disprivileged but they have some status and role to perform in society. They are made to perform very useful though degrading and defiling occupations in the society. They live in their own groups and derive emotional fulfilment among their kith and kin. The leprosy patients are rejected even by their kith and kin and they are physcially thrown out of the society into compulsory isolation. Whatever may be the reasons, even medical profession does not get interested in them in as much as there are more para-medical and social workers serving the leprosy patients and their cause than medical personnel. This is inspite of the fact that leprosy is primarily a medical problem and as a consequence, it has assumed complicated social dimensions.

Why social stigma is attached to leprosy? Is it because the people consider the disease incurable? It is because they consider it a hereditary disease? Or is it because they know of the disease as a disease of deformity? There are many other diseases which are more infectious, hereditary and bring about deformities. Small pox is also a dreaded disease though in Hindu society, it is hardly considered as a disease. They accept it as visitation of the mother goddess. Small pox sometimes brings deformity though not as severe as that of leprosy. The small pox has been too common. The progress of the disease has been known to all. It has been known to be curable or fatal. It manifests itself easily and cannot be concealed. A person cured of small pox is seen to be leading normal life. As a result of all these factors, no stigma has been attached to small pox. In contemporary western society, however, small pox marks could also be stigmatised though not comparable to deformities in leprosy. In western society, effective administration of small pox vaccine has made small pox extinct and hence the fear of a new case exists. The disease has been claimed to have been eradicated from India also. People used to be afraid of Tuberculosis also but there was no stigma except in marital matters. A tuberculosis patient evoked sympathy because the damage used to be internal and the exterier looked normal. Stigma cannot get

attached to a disease condition which may have to be commonly experienced by people in all walks of life.

A person might get deformities due to burns, or mutilations due to accidents. However no stigma is attached to the person possibly because there is no danger of his condition spreading to others. When we look at a person deformed due to burns, we are sure that we would not get it by looking at him or by touching him.

In case of leprosy, people equate the disease with gross deformities. People harbour prejudices due to ignorance about the disease. They do not know of the early signs of disease and about its slow progression. A person cured of leprosy, before he develops the signs such as nodules, does not reveal that he had leprosy and that he was cured. He keeps his experience a secret if he has been successful in taking the medicines secretly. This secretive behaviour is the result of peoples' ignorance about the curability of the disease. Even law makers talk of 'incurable and virulent form of leprosy' and make it a fit condition for divorce. People wrongfully associate leprosy with gross deformities and consider the disease hereditary. If such a disease which is 'incurable', 'hereditary' and also infectious, 'definitely resulting in gross deformities' would not be stigmatised, which other disease would be stigmatised? Thus, the ignorance and prejudices have helped the condemnation of a person afflicted with leprosy.

Unfortunately, drugs giving quick results have not been available, a preventive vaccine could not be prepared and even the epidemiology of the disease has not been clearly under stood. The leprosy bacillus is known for more than a hundred years. However, failure to cultivate it in the test tube has retarded the development of fast relieving drugs against leprosy. Unfortunately the disease does not always reveal itself to a person nursing it. When he comes to know of it, it has probably progressed enough to get him condemned by the society. The people are also ignorant about the fact that majority of the leprosy patients are non-infectious. Even the law givers reveal their ignorance on this point. So, the nature of the disease, slow progress of scientific knowledge, ignorance and/or indifference of the law givers and prejudices of the people help to make and keep leprosy a stigmatised disease.

The stigma is also due to the close relationship of health aspect of culture with the religious aspect of culture. Like many other diseases, leprosy also is considered as god's penalty for sin in almost all the societies. In every culture, there are certain socially acceptable ideas of body image. God is usually the embodiment of all perfection including beauty. People love the film heroes and heroines because they satisfy the aesthetic instinct. It has been found necessary to raise the slogans such as "Black is Beautiful" as an effort to change peoples' attitudes toward black people. In every culture, the idea of personal body image requires all the limbs of the body in right proportion and having the shape pleasing to the eyes. It is well known as to how women rushed for termination of pregnancies when they were told that a tranquiliser, Thalidomide could lead to the birth of deformed babies. Deformities are aesthetically displeasing and since a deformed person cannot become a productive worker of the society, he is not easily tolerated in the society. The problems of the handicapped need no repetition here. People thank god when a child with all the limbs in their proper places is born. A leprosy patient who is a deformed person in the eyes of lay people seem to have degenerated his limbs in his life time. People see a person born normal and then see him physically degenerate and suffer. Unlike in other untreated infectious cases, he does not die but he suffers. Death without suffering or with minimum suffering is preferred by people to suffering without death. Death is not considered as divine punishment for in most societies the idea of rebirth is prevalent. However, suffering is considered as divine punishment and there can be no worse mental suffering than suffering due to leprosy. According to Hindu concept of body image, human body is made of three elements, 'Satva', 'Raja', 'Tama' which are in the descending order from the standpoint of spirituality. Obviously, the disequilibrium in these three elements is believed to result in the disease condition. A disease like leprosy would probably result when the spiritual element gets completely lost from the body. In a culture, where spirit is at the end close to divinity as against matter, a disease condition resulting from loss of spirituality would obviously be detested.

A person afflicted with leprosy considers the future very bleak. He considers himself guilty of some sin if not in the present life,

in past life. He does not find any other explanation for getting leprosy. He knows that he would degenerate in body and would lose his limbs and nose. He feels certain that he would have to join the band of leprosy beggars whom he has been avoiding all these years. He therefore tries to hide the disease with the sense of helplessness and due lack of decision making. He accepts fate as it presents itself to him. This changes his personality and behaviour. In some cases, the person becomes a social deviant. By becoming deviant, he tries to put up a brave face by challenging the society. A person tries, in vain, to postpone social death by postponing treatment. Once isolated and caged in a colony, he accepts his social condition and tries to mix with his disease-brothers.

The society after identifying the leprosy patient starts rejecting him. He is denied civic facilities like public transport, educational and employment facilities. A patient is disowned by his kith and kin and thus his socio-economic ties with the society get snapped. Society is afraid of the spread of disease. As a result of lack of scientific knowledge on leprosy, society choses to sacrifice few individuals in the interest of the majority by killing the patients socially, by isolating them away from society.

Recently, the High Court of Tamilnadu had to direct the lower courts to record the evidence of leprosy patients in their respective courts. The matter arose because one of the Magistrates ordered the 'ex-leprosy patients' to go out of the court instead of recording their evidence as witnesses. The High Court referred to the conduct of the Magistrate as 'reprehensible' (NLO News letter, 1977: Vol. V, No. 4)

Law makes an effort to generalise the prevailing social customs for social good. Social legislation is also used as a tool to reform the society, to anticipate the change to be brought about in the society. The laws concerning leprosy in India were primarily enacted in the late nineteenth century and they continue to be on the statute books. The laws then did reflect the mood of the society. There may not have come a great change in social attitudes at the level of masses. However the medical sciences have advanced now. The change has come about in the treatment of leprosy. Infectious and non-infectious cases are now clearly distinguished. However, the law is blind and instead of reflecting the future, it continues to reflect the dead past. The leprosy Act of 1898 and the Railway Act of 1890 were based on the assumption that the disease was incurable and that all patients spread the disease. Special legislation about leprosy puts it in a special category. It demoralises a person from seeking treatment because he does not want to be subjected to law in health matters. If at all any legislation in regard to leprosy is required it is to protect the rights of leprosy patients as citizens of the State and to help them to be useful, productive members of the society. Protective legislation is being provided to help the socially and economically disprivileged sections of the society by making constitutional provisions. Leprosy patients also require some protective legislation. Such legislation will help the process of destigmatisation and rehabilitation. As all people are not delinquents, similarly, all leprosy patients are not vagrants. But providing legal action against leprosy vagrants give an impression in the society that leprosy is connected with anti-social activities. Leprosy patients are driven to beggary due to prejudicial attitude of the society. The problem of beggary or of leprosy beggary cannot be solved by removing them from the streets. In fact, the leprosy beggars who move isolated on the streets do not pose public health problems. At regular intervals, the idea is mooted about the compulsory sterilization of leprosy patients. Such measures would surely drive the leprosy patients to discontinue, or not start treatment and try to conceal the disease.

In India, Dissolution of Muslim Marriage Act 1939, special marriage Act 1954 and the Hindu Marraige Act 1955 provide clauses for separation and divorce on grounds of a spouse suffering from virulent form of leprosy for a certain period. The reasons for the incompatibility of the spouses may be many. However when the law selects leprosy and leaves all other infectious diseases, it clearly confirms the prejudices of the society towards leprosy. It would be therefore much wiser to do without any legislation regarding leprosy. That would help health education of the people. Law is an important social institution and it sets the trends in the society. World Health Organisation has also recommended leprosy to be treated on par with other communicable diseases by the law givers. In fact, these matters need to be taken care of by the Public Health Authorities and not by the law givers.

In India, the National Leprosy Control Programme of the Government of India has been trying in collaboration with the States to control leprosy in the country for the last 22 years. The assessment of the programme as reported by R. V. Wardekar, Chairman of the Gandhi Memorial Leprosy Foundation, suggests that the problem of leprosy has decreased in the areas where the programme has been effectively organised. However, there prevails a general sense of helplessness and despondency with regard to control of leprosy. The leprosy control programme has been channelised mainly through the leprosy control units and the Survey, Education and Treatment (S E T) centres. The emphasis has been on early case detection, mass treatment, case holding and to do all this effectively, health education. By and large, house-to-house survey have been recommended in rural areas and health education has been recommended in urban areas. In the urban areas, surveys are conducted in slums and schools.

However, it is felt that the leprosy control programme lack its feet and teeth due to apathy of the people and non-participation of the people in the programme. People are apathetic because they lack the knowledge of the early signs of leprosy and continue to harbour the prejudices about leprosy. Generally, the education part of the S E T pattern is neglected. Gandhi Memorial Leprosy Foundation initiated the establishment of Health Education Units in certain urban centres. The evaluation of the Health Education Programme of the Gandhi Memorial Leprosy Foundation reveals that Health Education does favourably change the knowledge and attitudes of the people towards leprosy. (Mutatkar; 1977). However, Health Education has not yet been taken seriously as an activity of the leprosy control programme. It has been seen that the medical practitioners have also been showing apathy towards the detection and treatment of leprosy in their dispensaries. The reasons have been attributed to lack of clinical confidence and the stigma of leprosy which affects the medical personnel also. Because of a large area of darkness about the knowledge of leprosy, many medical personnel want to keep themselves away from leprosy. This helps to increase the suspicion and prejudices of common people about leprosy.

It was considered necessary by the Gandhi Memorial Leprosy Foundation to offer refresher courses to the medical personnel. These refresher courses made them confident to diagnose and treat the cases in their dispensaries. A patient obviously prefers to discuss his health problems with his family physician instead of getting stigmatised by entering a leprosy clinic.

The leaders of the society need to be educated because they make the legislation about leprosy and influence public opinion. Not many specific attempts have been made to orient the political leaders. Leprosy control programme cannot be effectively administered unless it is whole heartedly supported by social and political leaders. These leaders, themselves the products of social environment also suffer from lack of knowledge about leprosy and share the prejudices with the people. The leaders who are supposed to mould the attitudes of the people need to be educated sincerely. Mahatma Gandhi as a social leader could motivate many workers to dedicate their energies to the cause of leprosy because he had educated himself about the facts of leprosy.

People do not come forward for early detection due to ignorance and fear. They do not continue treatment for long periods because the progress of cure is slow and the intrinsic conviction about the curability of the disease is lacking. The deformities striking to the eyes continue to perpetuate the stigma. The stigma bars the speed and seriousness of the control programme. The ultimate remedy in breaking this vicious chain lies in early detection, early treatment and preventing deformities. This is possible if people get to know the early signs of leprosy and if the medical profession encourages early detection and treatment in their respective dispensaries and clinics. The stigma will disappear only when the deformity will disappear. With the disappearance of stigma, society will start treating leprosy like any other communicable disease. This approach first propounded by Gandhi Memorial Leprosy Foundation would hold good till the medical know how of quicker recovery is developed or till the vaccine is developed. From the experiences of small pox, it however appears that we will have to promote the programmes which would lead to voluntary reporting on the part of patients, and prompt and prolonged dispensation of treatment by all medical practitioners. The rehabilitation, and support of law would save a leprosy patient from social death which ultimately will help to eliminate the stigma.

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APPENDIX

Lepers Act, 1898

The Indian Lepers Act of 1898 provides for (a) the segregation of beggars with leprosy, and (b) the control of leprosy patients following certain occupations or doing certain acts such as: (i) the preparation for sale or the sale of food, drink, drugs or clothing, (ii) taking drinking water from or bathing and washing clothes in the public wells and tanks, and (iii) the use of public vehicles, etc. This act is permissive Act which can be put into force in whole or in part by a notification by the Local Government.

THE CHANGING WORLD OF LEPROSY

Mr. A. D. Askew

"What holds true for the individual holds true for the society. It is never static: if it does not grow, it decays; if it does not transcend the status quo for the better, it changes for the worse ... The moment we stand still we begin to decay."

Erich Fromm.

Change is an essential part of life; where there is no change, there is death. Change can be disconcerting, but if we are to respond adequately to the needs of leprosy sufferers and to the needs of the leprosy programme, change is essential.

The Last Twenty-Five Years

My own career in leprosy work began in November 1950 when I joined The Leprosy Mission staff at Purulia, in West Bengal, and worked there for fifteen years. Looking back to the 1950s one remembers the optimism of the early days of sulphone therapy. At last there was real hope. Individual patients were declared disease-arrested, cured. Prophets arose and produced slogans which suggested, even promised, that leprosy could be controlled within one generation, and perhaps eradicated in two.

Certainly there have been great and stimulating changes in the way we deal with leprosy. Stemming from the introduction of sulphone therapy, and the new and dramatic hope brought by increasing knowledge of the remedy and prevention of deformity, leprosy treatment has changed almost beyond recognition. The static, inward-looking asylum has become a hospital, patients who were previously isolated for years now move through hospital in a matter of weeks or months and back to their community. Most indeed never need to see a hospital at all. In the 1950s there were some who felt that leprosy centres were no longer required at all, that everything could be achieved by village clinics. This radical pendulum swing has now moved back into balance, and the centre has become smaller, but also the dynamic base for an organised network of village clinics, paramedical workers and supporting facilities and personnel.

The change has been a hard one, and has sometimes been more traumatic to leprosy workers than to patients! There are still places where the change is not complete, but the re-orientation process has gone a long way. These changes have brought greater hope to patients than ever before, education is slowly changing social attitudes, and greater interest in the problems of leprosy is being shown in many quarters.

Today, governmental concern in most countries is stronger than ever before. Many countries have created their own national leprosy organisations to coordinate the efforts of official and voluntary agencies. Many new voluntary agencies have come into existence. The International Federation of Anti-Leprosy Associations (ILEP) now comprises 24 full members, ranging from the USA to Japan, all promoting leprosy work, and raising funds for use internationally. Long gone are the days when organisations like The Leprosy Mission stood alone. Today there is more cooperative consultation, planning and work than ever before.

Yet, in spite of the slogans of twenty-five years ago, leprosy is still with us, and successive estimates of the prevalence of leprosy suggest larger figures. World estimates of leprosy have always been approximations, and are usually based on incomplete and insufficient data modified by experience. Usually conservative, still the tendency is to higher figures. Whether leprosy worldwide is increasing, or whether the higher estimates simply reflect more accurate information cannot be said with any certainty but it can be said that there is no evidence to suggest any fall in total numbers.

The Present Position

1. Efficient, conscientious medication can return patients to society disease-arrested, under control, and with hope restored.

2. Training of patients can prevent much deformity and avoid many of the social and vocational problems which disablement brings.

3. Physiotherapy and techniques of reconstructive surgery can remedy and remove some of the physical stigmata of leprosy, restore function and allow disabled patients to contribute economically to their community.

4. Demonstrations of the effectiveness of modern medicine in curing disease, coping with complications and preventing the spread of infection can, coupled with health education, change community attitudes towards the leprosy sufferer.

5. Resources, in personnel and finance available for leprosy work, are growing, although the latter may be swallowed up in many countries by the effects of inflation or the cost of leprosy control, as well as the future need to use costlier drugs to combat sulphone resistance.

6. More patients are registered and under treatment than ever before, and the numbers continue to rise.

Yet leprosy is still with us.

The Need for Re-appraisal

In spite of widening knowledge over the whole field of leprosy studies, of the immense practical efforts of the last twenty-five years, and in spite of the increased facilities for the growing number of patients under treatment, the situation calls for an urgent and sober re-appraisal.

1. There is growing evidence that leprosy is not being 'contained'. Treatment and control programmes have not reduced the prevalence of leprosy, and most countries are far from any real control of the disease.

2. Approximately 80% of sufferers from leprosy still receive no medical care at all.

3. Where treatment is available, it is often made ineffective by a combination of irregular attendance, a high drop out rate, and continuing social prejudice and pressures against the disease.

4. There is growing evidence of the development of strains of *M.leprae* resistant to sulphone. This problem has probably been with us for some time, but is now being reported with supporting proof, from a number of areas. Arising from irregular treatment and, probably, from low dosage regimes this problem makes it imperative that accepted methods of treatment and control should be re-examined with care.

The picture, then, is one of potentially effective treatment having less effect than it should have through a variety of circumstances which need to be analyzed and understood, so that the appropriate changes can be made in response to them.

The two greatest dangers are complacency and dogmatism.

Complacency

It is easy for the leprosy worker—paramedical, nurse, doctor or administrator—to be satisfied with superficial statistics which show a rising number of patients found and registered for treatment. Many workers are so preoccupied with these numbers, and with the actual medical care of those who attend, that there is no time or inclination to analyze what is actually taking place, nor to plan activities directed at influencing events.

Modern management, with its emphasis on aims and goals, and the careful appraisal of results, has much to teach us in organising our work. It is a cause for concern that many leprosy centres have no clearly thought-out policy and goals, other than the general one of "treating as many leprosy sufferers as possible". There is need to look carefully at the field of work in front of us, and at our resources, and in what area we can best apply them. This may be defined in terms of the geographical or population limits within which we will work, or in deciding on the particular type of service we can offer, e.g. leprosy control, rehabilitation or other services, or a combination of several.

A more thoughtful and thorough analysis of real statistics is also necessary to discover what effect, if any, a piece of work is really having. For example, is the number of patients who attend irregularly increasing or decreasing? What percentage of patients under treatment drop out within 1, 2 or 3 years? (If it is a large percentage, then much of our time, effort and resources are being wasted, apart altogether from the danger of encouraging the development of sulphone resistance.) What are the reasons for the irregular attendances and drop-out? What changes can be made in our organisation and approach to improve the situation? It used to be said that the static leprosarium did nothing to diminish the reservoir of disease or break the cycle of infection, and that only outpatient clinics would do this. The point was a good one, but today we must admit that many outpatient treatment programmes are "static" in the sense that they also do little to reduce that same reservoir of disease and its consequenct suffering. In the days ahead, emphasis must be placed on quality and effectiveness of service rather than on sheer numbers, as a means to real progress.

Another question must be asked. Do the expensive, time-consuming total population surveys carried out in many countries achieve what is expected? Frequently, only 80-90% of the population is covered anyway, sometimes less. And is there any practical value (apart from the intrinsic value of statistics) in *knowing* the total number of leprosy patients in the area unless they are brought under treatment and so *motivated* that they are *held* under treatment? Does total population survey achieve a greater percentage of patients under regular treatment than a network of village clinics coupled with an effective health education programme? It would be instructive to know.

Dogmatism

Each new insight into leprosy treatment is hailed as the ultimate answer to the problem.

For many years, workers believed that leprosy control could be achieved by isolating infectious cases, either in leprosaria, or through home segregation or night-segregation. The coming of sulphone brought the proposal that mass campaigns—the widespread distribution of sulphone, often without supporting facilities of any kind—would control leprosy in one or two decades. A widely advocated corollary was that time and money spent on ulcer care, shoe programmes, and surgery was wasted. Concentration on early treatment would lead to control without the other services. It is now realised that these ancillary services are vital, because motivation of patients must include meeting their felt needs and often the need the patient feels is not for a small white tablet to combat an unseen and not well-understood infection, but the need for a remedy for his plantar ulcer, or an understanding of anaesthesia and why he keeps damaging his hands. Without this, confidence in his basic sulphone therapy evaporates and he joins the ranks of those we label 'absentee' or 'defaulter'. A later proposal was made that when it was very difficult to treat all leprosy cases in an area, proirity should be given to treatment of lepromatous cases in order to reduce their bacillary load. Even if treatment was intermittent it was said that it would reduce the load to some extent and thus do some good, by limiting the number of highly bacillated patients who were spreading the disease. With the wisdom of hindsight, the emergence of sulphone-resistance suggests that this proposal was not a very felicitous one.

And so one could go on. The purpose of these comments is not to deride past theory and practice because much has been learned through the application of such methods, and progress cannot be made without error. The purpose is to reinforce a plea against the dogmatism which catches hold of the latest, fashionable theory, and promotes it to the exclusion of all else.

Recently emphasis has been placed on the integration of leprosy into general health services. The proposal is logical and may well be correct if it is achieved at the appropriate point in the evolution of health services within a country. But its uncritical acceptance has, in some countries, resulted in the unloading of responsibility for leprosy treatment onto unwilling cadres of general medical workers, without the necessary training and skills. The result can be the setting back of leprosy control by many years.

Again, the emphasis must be on the careful appraisal of dogmatic assertions, the recognition that what may be appropriate in one set of circumstances is not necessarily so elsewhere, and that an essential pre-requisite to further progress is innovation: freedom to modify present programmes and to experi-

ment (responsibly and with due regard to the well-being of our patients) with new ones.

It is at this point that voluntary agencies have an advantage over governmental ones. While Voluntary Agencies must cooperate willingly and fully with government, the V.A. has an inherent flexibility which government health services lack by their very nature. Frequently, innovation will be part of the V.A.'s responsibility, and the role of a wise administration will be to allow V.A.s sufficient initiative and freedom for the development of new ideas.

An example of the new approaches which require to be made is the present need for deep and sensitive study of the leprosy situation through the patients' eyes and feelings. Modern behavioural insights, relating both to individuals and to groups, can help us to a deeper understanding of motivation, education and e.g. the real underlying causes for irregular attendance. It is not enough to make treatment available. We need to know why patients do not always accept it.

The Future

In predicting the future it is important to guard against the dogmatism which has already been criticised above. The following suggestions are made with some knowledge both of present trends, and of weaknesses present in some leprosy programmes today. Tomorrow's leprosy programme will need to include:

1. *Control in depth.* Present staff: patient ratios, e.g. one paramedical worker to 25,000 rural population, may have to be revised in the direction of more staff in order to achieve better motivation and supervision of patients under treatment. Closer follow up of absentees, the achievement of better attendance records, will be essential, not only for the good of the individual patient, but also to lessen the risk of further development of sulphone resistance. This will inevitably lead to higher costs, but may also lead to more effective control of leprosy than present methods have achieevd.

2. *The use of Alternative Drugs.* Wider use of the present alternative drugs will probably be essential to combat sulphone resistance. The present alternatives are expensive (clofazamine) or very expensive (rifampicin). Their use will have to be carefully debated, assessed and controlled, but inevitably they will be needed, unless newer and cheaper alternatives can be found.

3. *Coordination of Research.* Commendable efforts have already been made by WHO in coordinating research into immunology and the possible development of a specific vaccine (through IMMLEP) and in chemotherapy (THELEP). More will be needed, with continued efforts by National governments, WHO, and Voluntary Agencies.

4. *Training.* Standards of training, and of trainees, is improving steadily. There are more recognised centres for training workers now than ever, but with little coordination or comparison of standards of training between one centre and another. This needs remedying.

   Training centres concentrate largely on the initial, basic training of doctors, paramedical workers and others. Insufficient thought has been given to refresher courses, re-training and further training. For example, at present paramedical workers, usually 20-30 years old, are given 6-8 months' initial training and are then expected to give many years of service, often demanding considerable initiative, dedication and relative isolation in rural areas. As the spearhead of leprosy control their motivation and encouragement is essential. Regular referesher courses will be needed, together with a more carefully and clearly defined career structure which recognises hard work and talent, and rewards it with higher responsibility and job satisfaction.

5. *Improving Standards of Care.* The need to develop and maintain better supportive services for leprosy sufferers is urgent. Only when control programmes deal adequately with the complications of a patient's condition, and his social problems, will the effectiveness of our programmes improve. Improved standards of care do not call for more lavish buildings or expensive medical equipment, but for a better understanding of the patients' needs, better training, and the willingness to help.

6. *More and Better Education.* Education still has to begin with doctors, nurses, and others who form or influence public opinion and reaction to leprosy, but must permeate right through the community. Increasing the techniques of communication and the use of mass media will be used, but these will never replace the observed behaviour of leprosy workers towards their patients.

All these will play a part in progress towards control of leprosy, and all of them will call for changes in our work. The criterion for judging change must be whether or not it is for the good of the patient and the programme rather than how it will affect the worker. We are here to serve the sufferer, not to perpetuate our own methods or status. And it is the welfare of the patient that we must continually watch.

Treating the Patient as an Individual

The well-being of individual patients is not an optional extra to which we occasionally turn the attention of our social worker, if we happen to have one on the staff. The single, most important factor in effective leprosy treatment, today and tomorrow, is what the individual patient feels about the worker and the treatment he is given. Good buildings and equipment, trained personnel, and reliable vehicles contribute much to a leprosy treatment scheme, but if the service they deliver is cold and impersonal, if the patient is treated only as a number in a register, and if improvement is not *seen* to be taking place, the scheme will not be effective. Long term, regular clinic attendance depends on establishing and maintaining the patients' confidence in the staff and the care they offer.

Confidence is built up by good human relationships. The greatest damage which leprosy causes is not plantar ulceration or clawhand, but the destruction of human dignity and the devaluation of personality. This must be remedied in the mind of the patient himself, and in the collective mind of the community by respecting the patients dignity, by efficient medical care, by effective and understanding community education, and by accepting and treating the leprosy sufferer's needs in terms of his full personality, body, mind and spirit. For full health the patient needs medicine, the opportunity to contribute something of value in his community, and a living hope for the future. Change must be directed towards the fuller achievement of these things.

THE WORLD HEALTH ORGANIZATION IN LEPROSY CONTROL

H SANSARRICQ[a], J WALTER[b], K S SEAL[c]

The role of the World Health Organization (WHO) in combating any disease which represents a public health problem is essentially determined by the World Health Assembly through successive General Programmes of Work. Within this framework, WHO acts accordingly on requests of individual governments, subject to availability of budgetary resources.

In July 1948, the First World Health Assembly decided that leprosy should be given number six priority. A panel of experts on leprosy was set up in 1950, and the First Expert Committee on Leprosy was convened in 1952. The Leprosy Unit in the Headquarters of WHO was established in 1958.

The WHO General Programmes of Work are established for five-year periods. WHO's Fifth General Programme of Work covering the period 1973-1977 inclusive, and the Sixth (1978-1983) refer to leprosy as a communicable disease of major public health importance. In Africa (excluding North Africa), the Americas and Asia, governments of developing countries considered leprosy as a public health problem in 1957-1960 and again in 1965-1968[1]. The Sixth General Programme of Work states that "leprosy will be the subject of an increased research effort under a special international programme for tropical diseases as well as under national control programmes in which the Organization will cooperate".

The Twenty-seventh, Twenty-eighth and Twenty-ninth World Health Assemblies in May 1974, May 1975 and May 1976 adopted three resolutions on the coordination and strengthening of leprosy control, as well as on the intensification of research activities.

For a better understanding of the WHO role in leprosy control we would like first to recall briefly the WHO organizational framework. In WHO structures there are three levels: (a) country, (b) regional, and (c) global.

The country level corresponds to the national programmes where the WHO contribution is based on the role of the WHO representative, who is the focal point for all activities involving WHO cooperation.

The regional level is represented by the six WHO Regional Offices in the different WHO Regions (in Brazzaville, for the African Region; in Washington, for the American Region; in Alexandria, for the Eastern Mediterranean Region; in Copenhagen, for the European Region; in New Delhi, for the South-East Asia Region; and in Manila, for the Western Pacific Region).

The global level is symbolized by the WHO Headquarters in Geneva.

The Regional Offices provide their assistance to control activities in countries on governments' requests. As for Headquarters, it is in charge of the research programme in its definition, and then for providing support to institutions which, in different countries, are implementing individual research projects. In addition, Headquarters is responsible for overall coordination, and ensures particularly that technical orientations are maintained in conformity with the most recent advances in knowledge through Expert Committees or Study Groups.

There is a growing and welcome trend for more emphasis to be given to direct technical cooperation at the country level. In addition, efforts are made to decentralize WHO coordinating activities giving more importance to the role of the Regional Offices particularly in the WHO research programmes. The responsibility for leprosy

[a] Chief Medical Officer, Leprosy Unit, WHO, Geneva, Switzerland

[b] Medical Officer, Leprosy Unit, WHO, Geneva, Switzerland

[c] Plymouth, England

control activities has rested with Regional offices for some years already.

We will now discuss the different WHO activities relevant to leprosy control under the six following headings:

1. Assessment of the leprosy problem;
2. Policy guidance;
3. Coordination;
4. Technical cooperation;
5. Manpower development;
6. Research.

1. Assessment of the leprosy problem

The actual number of cases requiring treatment in the world remains difficult to estimate.

The first attempt to provide realistic figures of the number of leprosy cases in the affected countries of the world was made in 1966[2]. The data used were based primarily on the figures given in reply to a WHO questionnaire supplemented by various reports of WHO staff and consultants, data from literature and official reports published by governments or international organizations. The low level of the case-finding in most countries and the generally poor health information systems then existing clearly indicated that the totals of the reported cases were far less than the true total. The extent of some of these divergences was demonstrated by the survey work of the WHO Leprosy Advisory Team in a number of countries of Africa, Asia and South America. From the experiences of this team an arbitrary multiplication factor was devised for calculating total estimated cases from registered cases which depended on an evaluation of the efficiency of the case finding and the coverage of the country by health services.

Thus, in 1966 there were 2,831,755 registered patients of whom it was estimated that 68% were actually receiving treatment. A conservative estimate of the total cases throughout the world was 10,786,000, suggesting that only about 18% of the total estimated patients were receiving treatment.

A review of the situation by WHO in 1970[3], when improved data from some national leprosy control programmes became available, gave no grounds for thinking that the total number of cases throughout the world had changed significantly. Thus, the number of leprosy cases estimated by WHO in 1970 by continent was as follows:

Africa	3,509,000
Americas	344,700
Asia	6,471,400
Europe	49,300
Oceania	32,800
Total	10,407,200

In addition, it was estimated that as many as 33% of all registered patients, in global figures about four million, may be expected to have some disability, and of these two million were suffering from a severe deformity of face or extremities.

A numerical appraisal of the present day situation is scarcely less tentative than that of 1970 because so few countries have accurate reporting systems for leprosy.

There is an urgent need, if an accurate picture of leprosy prevalence is to be gained, for a comprehensive and standardized system of reporting, and WHO has already commissioned and completed an analysis of currently used leprosy information systems throughout the world. An information system is now being developed which will provide data for epidemiological surveillance and which will be simple enough to be generally acceptable by countries and can be an integral part of the projected general WHO Information System.

Apart from the inaccuracies of data collection, some consideration has to be given to the following important facts.

(1) The rapid expansion of the population in those countries where leprosy is most commonly endemic increases the number of persons at risk of exposure to the disease. It is not known whether the incidence of new cases has increased or whether there is a rise in absolute numbers. The Fifth Expert Committee on Leprosy, 1976[9], stated that the overall reductions in the number of leprosy cases achieved by leprosy control measures in recent years may have been offset by the greater numbers of persons at risk.

(2) In a number of countries with leprosy programmes, the official statistics show little reduction in the total number of patients

receiving treatment. This is in part due to the reluctance of health staff to discharge patients who have received adequate and successful treatment. This is believed to be true in several countries in West Africa and South-East Asia. In fact, random sample surveys in countries such as Burma (1974), Thailand (1973) and Upper Volta (1974-77) have shown prevalence reductions of 70% to 75% over ten to fifteen year periods.

During 1976, questionnaires were again distributed by WHO through Regional Offices to countries to assess the leprosy situation. Full results are not yet available and, while some countries report a reduction in prevalence, any global appraisal of the situation must await complete analysis of the returns. However, in 1975, the WHO South-East Asia Regional Office collected updated information which is given in Table 1.

TABLE 1

SOUTH-EAST ASIA REGION

SUMMARY OF DATA CONCERNING GEOGRAPHICAL DISTRIBUTION OF LEPROSY IN SOME COUNTRIES OF THE REGION AT 31 DECEMBER 1974

Country	Pop. Census year	Registered[1] cases	Estimated cases in thousands	Overall prevalence per 1000
Bangladesh	41,479,071 (1974)	18,100	200	5.0
Burma	28,885,867 (1973)	248,742	500	17.0
India	547,000,000 (1971)	1,320,000	3,200	5.8
Indonesia	129,083,000 (1974)	97,197	230	1.8
Maldives	131,857 (1975)	1,339	2	15.0
Nepal	11,555,983 (1975)	11,614	38	3.25
Sri Lanka	14,000,000 (1975)	7,860	14	1.0
Thailand	45,000,000 (1975)	43,616	120	2.6
	955,135,788	1,748,468	4,304	—

1 The cumulative number of released from control cases is difficult to obtain and could not be included in this column. The difference between registered and estimated cases would therefore not be deducatable from this table.

2. Policy guidance

The technical policy of WHO in the field of leprosy, as well as in other diseases, is laid down in WHO Expert Committee recommendations. Expert Committee meetings on leprosy have been convened, in addition to the first 1952 meeting, in 1959, 1965, 1970 and 1976.

The main way by which these technical orientations are disseminated is the publication of technical reports. For leprosy, each of the five Expert Committee meetings resulted in the publication of one of these technical reports [5, 6, 7, 8, 9]. Of the 1st to 4th Expert Committee reports, some 24,000 copies have been distributed.

Similarly, the Leprosy Unit published a Guide to Leprosy Control in 1959 which was revised in 1966. More than 2500 copies have been distributed.

In 1952, the Expert Committee recommended the abolition of compulsory isolation of leprosy patients, and that leprosy control should be based on early detection and ambulatory regular treatment of patients[5]. Later on, WHO emphasized increasingly the abolition of isolation.

In 1965[7] the Expert Committee advised that countries with limited resources should concentrate their efforts on treatment and follow-up of infectious cases and on surveillance of their contacts.

Since 1962 increasing emphasis has been put on the need to integrate leprosy control programmes as much as possible within the activities of the general public health services.

We shall now discuss in more detail the Fifth meeting of the WHO Expert Committee on Leprosy, which was convened from 19—25 October 1976. Preparations for the Committee began with informal consultations with 57 members of the Expert Advisory Panel on Leprosy. The views of experts in tuberculosis and public health were also sought, bearing in mind the need for leprosy control to be an integrated service within the general health care system.

The Committee, after a review of the present situation, has sought to give guidance in the programming and management of leprosy control[9]. Particular emphasis has been given to the manpower formation aspects, the deployment of staff and the supervisory organization, and of the assessment of the activities by the fixing of operational milestones and output targets, and by the definition of the most important operational and epidemiological indicators.

In the area of chemotherapy, the Committee was confronted with two major problems of dapsone resistance and microbial presistence. To meet these hazards, the Committee made recommendations for combined regimens, keeping in mind economic considerations, involving the use of clofazimine and rifampicin to be introduced for multibacillary cases only.

The vital need for adequate information at national level on leprosy prevalence and morbidity was reflected in the recommendations. As a first step to meeting this need, an analysis was made by a collaborating centre of the various individual clinical records and reporting forms used by 78 control services in 45 countries of Africa, Asia, the Americas, Oceania and the Philippines. It is planned to develop a system which will provide standardized information of an elementary nature, collected directly by health staff at peripheral level. On the basis of these data national figures can be derived and used at Ministry level to allow an assessment of the programme.

From these recommendations the principal approach to leprosy control will be:

1. The improved programming and management of leprosy control activities.
2. The development of multidisciplinary manpower.
3. The gradual build-up of an integrated country level information system.
4. The strengthening of research activities, particularly those to be carried out within the WHO Special Programme for Research and Training in Tropical Diseases.

3. Coordination

3.1 UNICEF

In 1953, the UNICEF/WHO joint Committee decided to include leprosy among the diseases for which both Organizations would provide coordinated assistance. Following this decision, while WHO has continued to provide expert services, UNICEF has supplied drugs, equipment and vehicles.

The Report of the Twenty-first Session of the UNICEF/WHO Joint Committee on Health Policy, 21 January—2 February 1977, "emphasized that communicable diseases are still of paramount importance in the developing world", and affirmed the necessity for commitments of 5-10 years if the proper actions in this field can be undertaken at country level. Leprosy falls within the group of diseases in which control is being attempted by chemotherapy. Experience shows that a well conducted active case-finding and case-holding programme can confidently expect to produce a substantial fall in the prevalence and of possibly the incidence of new cases within 10-15 years.

The Joint Committee has recommended the principles of primary health care as a commitment in their collaboration with countries, special emphasis being placed on community participation. The latter has always been a tenet of leprosy control programmes and is essential for success in control.

UNICEF assistance to leprosy programmes has two components, a major one of supplies and equipment, comprising transport, medical equipment and drugs, and a smaller component in cash terms representing stipends for trainees in the lower echelons of health staff.

3.2 Cooperation with Non-Governmental Organizations (NGOs) and multilateral agencies

(a) Non-governmental Organizations

A close relationship has been maintained for many years between the International Leprosy Association (ILA) and WHO. Although the ILA has a very limited budget it has considerable and important connexions with other foundations and voluntary agencies. Expert assistance for both WHO and ILA are drawn from the same professional pool.

Technical and scientific committees of the ILA, and to a similar degree also of voluntary agencies, have a profound interest in the public health approach. Routine use is being made of the ILA medium (the International Leprosy Journal) and of ILA sponsored meetings for publicizing WHO policies, objectives and programmes.

It is of special interest that the International Union Against Tuberculosis has recently started cooperating with the International Federation of Anti-leprosy Associations (ILEP) and other voluntary organizations with the aim of supporting programmes of either tuberculosis/leprosy combined activities, or integrated public health programmes with tuberculosis and leprosy components.

(b) Voluntary agencies

The International Federation of Anti-leprosy Associations (ILEP) which represents over 24 voluntary agencies from 16 donor countries, maintains close cooperation and liaison with WHO. As an expression of this long-term liaison mechanism, the Fifth WHO Expert Committee on Leprosy (1976) recognized that a large proportion of leprosy patients at present are treated by voluntary agencies and made specific recommendations on the role of voluntary bodies in national leprosy programmes and technical cooperation[9]. There is now a general appreciation among voluntary agencies seeking to help patients that their action should be an integral part of, or closely coordinated with, government programmes. In several countries such as India, the Republic of the Maldives, Indonesia, Nepal and in some African countries like the Sudan, ILEP member agencies are providing valuable contributions to the development of rural and urban community based health facilities.

Research has a high priority as also has training. ILEP supports seven training projects, of which three are institutions providing courses at international level: Ethiopia (ALERT), India (Vellore) and Liberia (Ganta). Rehabilitation continues to be a particular concern of ILEP member associations.

The efficacy of the services provided by voluntary agencies in the context of public health depends greatly on the support and recognition given by governments to their work. Full participation by the responsible staff of the voluntary agency in the planning and organization of the leprosy services nationally fosters good cooperation and coordination of effort.

This can often be achieved by the establishment of a National Leprosy Consultative Board or Committee, which may in large countries be formed at regional levels. Such an Advisory Board heightens the interest in leprosy control as a national goal, leads to a better appreciation of the needs of each area and hence to a wiser allocation of total resources.

Many countries benefit from the resources of voluntary agencies not affiliated to ILEP, and some have nationally established Leprosy Foundations.

4. Technical cooperation with governments

The Headquarters Leprosy Unit provides information, coordination and programme support services. At Regional level, the American Region has an Adviser on Leprosy and Venereal Diseases, and the Western Pacific Region an Intercountry Leprosy Control Adivsory Services Team for the South Pacific established in 1976. In the Africa and South-East Asia Regions, which include the countries most affected by leprosy, there are medical officers with special qualifications in leprosy.

Since 1950, WHO has cooperated with governments in about 50 leprosy control projects. In practice this cooperation was often achieved through field advisers working in close cooperation with nationals who took over the responsibility of the programme when the WHO experts left. This period of direct technical cooperation by the Organization with field advisers to assist in the development of leprosy control services had been phased out by 1970. There are still, however, a few WHO field staff in countries where particular circumstances have made their appointment or retention desirable.

With these exceptions, regular budget funds for country technical cooperation are used to provide the services of short-term consultants, fellowships, and a small component of supplies and equipment.

The present situation can be summarized as follows :

4.1 Africa Region

In the Africa Region, leprosy control services are integrated into epidemiological or strengthening of health services projects and do not appear in the WHO Programme Budget as leprosy advisory services.

In Upper Volta, the Government and WHO have cooperated with a number of voluntary agencies in a combined leprosy/tuberculosis random sampling survey, which has recently been completed (1977). This was of particular value in confirming the considerable reduction in the prevalence of active cases (75% reduction) resulting from the intensive antileprosy activities by mobile units in past years. The results of this assessment indicate that other countries, namely, Ivory Coast, Benin, Niger, Mali, Mauritania, Senegal and Togo, which have pursued similar programmes within a subregional Organization, the Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies (OCCGE), and Chad, Central African Empire, Cameroun, the Congo, similarly cooperating within the Organisation de Coordination pour la Lutte contre les Grandes Endémies en Afrique Centrale (OCEAC), might also find a significant decline in the true prevalence.

The same Upper Volta project sought to explore the feasibility of combining leprosy and tuberculosis activities in the field. This approach is being increasingly used, for instance, in Venezuela, Bangladesh, Nepal and the Maldives, and may have wide application for many countries both in Africa and elsewhere.

4.2 America Region

In the ten-year health plan, 1971-80, those countries which considered leprosy to be a national problem have set themselves goals for 1980 in the reduction of prevalence.

Technical cooperation for the development and evaluation of leprosy control services is provided through the services of a WHO leprologist based in Caracas and through the PAHO/WHO International Centre for Training and Research in Leprosy and Related Diseases, also in Caracas.

4.3 Eastern Mediterranean Region

During 1976, one country had consultant services, supplies and equipment, as well as fellowhips ; another entered upon the opening phase of direct field assistance by a medical officer ; a third received supplies and equipment.

4.4 South-East Asia Region

In 1975, a Regional Committee Resolution "emphasized the urgent need for coordinated and concerted efforts on the part of the governments, international and voluntary organizations and bilateral agencies to come to grips with the problem of leprosy within a short time". Consequent upon this, an Intercountry Consultative Meeting on Leprosy was held in New Delhi in December 1975, at which representatives from seven Member States reviewed the magnitude of the problem,

strategies for control and areas for research[4]. Targets were laid down for case detection in endemic areas, for treatment delivery and for intensification of population coverage. Collaborative field studies were planned on the reduction in bacterial load in lepromatous cases produced by different drug regimens including combined therapy.

The WHO BCG trial in Burma was terminated. In the same area consultants have assisted the Government, with Regional Office support, to develop a research design for a rifampicin clinical trial, and long-term results of the BCG trial are being evaluated.

In this Region, WHO is at present cooperating with the governments of five countries in the strengthening of their leprosy control activities. Among these, India intensified its case-finding and case-holding services to the hitherto unsurveyed high and moderately endemic areas.

In those countries (Burma, Thailand) where, because of the high endemicities, specialized leprosy control services were established, operational studies are now being conducted to ascertain the best way in which integration with the health services can be effected.

4.5 Western Pacific Region

As from 1977 a Regional Leprosy Advisory Team has been established for the next three years to undertake epidemiological and assessment surveys, and to guide health authorities in the operation of leprosy programmes in the South Pacific. This is the most effective approach for widely dispersed territories, and will create an efficient information system with the prospect of regular appraisals.

WHO cooperates with the governments of two countries in their leprosy control programmes.

5. Manpower Development

In recent years many countries have built up their own training institutions for the instruction both of general health and specialized staff, particularly of paramedical and auxiliary personnel.

Three hundred and one fellowships were awarded during the period 1960-1974. The distribution among the Regions being : Africa, 127 ; America, 76 ; Eastern Mediterranean, 28 ; South-East Asia, 106 ; and Western Pacific, 52. By 1976, awards had fallen to six. With the establishment of a Regional Training and Research Centre at Caracas (Venezuela), and well-established centres for Africa in Addis Ababa (ALERT), Dakar (Senegal) and Ganta (Liberia), and for South-East Asia in India at Chingleput and Karigiri, well organized formal courses of international standing are available for the health staff of all endemic countries.

Regional seminars and inter-country group educational activities have since 1958 been invaluable for training the higher echelons of national public health staff and in an exchange of views on strategy and leprosy control activities. More recently the WPRO has combined these seminars with tuberculosis (1969 and 1974).

There is need for a long-term plan for manpower formation in most countries and to implement such plans up-to-date trained teachers for leprosy control are required. WHO technical cooperation in this area would be of great practical use, and provision has been made for this in 1978 and 1979 in the regular budget.

An International Workshop on Leprosy Training in Asia took place in Bangkok (25-29 November 1976) with representatives from ten Asian countries and from various voluntary agencies (ILEP). The Workshop was sponsored jointly by the Government of Thailand and the Sasakawa Memorial Health Foundation (SMHF) with the technical participation of WHO. It stressed the need for raising the quality of country level training. As a first practical measure, a fact-finding mission will be assembled in 1977 to visit leprosy and other training institutes including Schools of Public Health in the various countries ; to identify existing or potential leprosy/public health training centres suitable for international training ; to make an estimate of the training needs for leprosy control for the coming five years—the needs being established as part of or within the country health manpower formation requirements.

A Workshop on the Chemotherapy of Leprosy was held in Manila from 26 January to 2 February 1977. This meeting was initiated by SMHF and jointly sponsored by the Government of the Philippines with WHO technical cooperation. This Workshop made practical recommendations on various regimens of combined chemotherapy for patients with the multibacillary forms of leprosy, which were consistent with the recommendations

made by the Fifth Expert Committee on Leprosy, October 1976.

It is the intention of the SMHF to sponsor further Workshops in cooperation with governments in Africa, Asia and South America.

6. Research

The limitations of the available means for leprosy control have become evident over the years, and it has been WHO's continuous concern to stimulate research aimed at providing better methods for the reduction of the leprosy problem.

In the last two decades WHO has supported collaborative research in the entire field of leprosy including studies on the biology of *M. leprae* and attempts at its cultivation, development of animal models, drug trials, diagnostic procedure and pathology of the disease. Special consideration has been given to the possible preventive action of BCG vaccine through a trial started in Burma in 1964 covering about 28,000 children under 14 years of age and still being followed. In this trial, protection was found to be limited to about 20% of the children between the ages of 0-14 years ; in addition the trial has enabled valuable epidemiological data to be collected.

Operational studies have been an important feature in a number of national programmes in recent years. For example, sample surveys have provided not only valuable epidemiological information and operational data for evaluation, but they have led to improvement of field strategies, and diagnostic methods. They have also contributed to the strengthening of health education and an appreciation of the psycho-social consequences of the disease.

The overall approach to the present WHO programme for research in leprosy may be subdivided into two main parts. One is undertaken within a WHO Special Programme for Research and Training in Tropical Diseases by means of what is called scientific Working Group Strategy, i.e. a multidisciplinary approach with a plan of work defined in advance to which all participating investigators have agreed. In addition the WHO financial contribution to individual projects selected by the Steering Committees of different programmes are fairly substantial. The second approach is by research agreements with individual investigators involving the provision of token grants.

6.1 Global programmes

Within the special programme for Research and Training in Tropical Diseases, priority is being given to two main lines of research in leprosy immunology and chemotherapy.

6.1.1 Research in immunology (IMMLEP)

The objectives of the programme are :

— vaccine development

— diagnostic test development (subclinical infection)

— exploration of immunotherapy.

An important prerequisite for this programme has been to obtain adequate supplies of *M. leprae* for experimental purposes. This has been achieved by increasing the supply of *M. leprae* from infected armadillo tissues to meet requirements. The other main achievements of this programme so far include purification of *M. leprae* and preparation of antigenic fractions and their evaluation, induction of immune responses in animals, studies on environmental mycobacteria antigenically related to *M. leprae*.

The scientific progress made over the past three years strengthens the initial hopes that a vaccine effective against leprosy can be developed ; yet it must be recognized that fulfillment of that goal for practical, large-scale application cannot be expected in the immediate future.

Possible ways of strengthening research capability in leprosy endemic countries include :

(a) wherever possible, research fellows in the IMMLEP programme should come from leprosy endemic countries;

(b) increased local training of personnel for field activities is important for future epidemiological or vaccine studies ;

(c) meetings of the IMMLEP Scientific Working Group might be held in conjunction with training courses in leprosy endemic countries.

6.1.2 Research on chemotherapy (THELEP)

THELEP has defined four broad objectives :

— to assess more accurately the risk of the emergence of drug resistant *M. leprae* during

single dose regimens with dapsone in lepromatous patients ;

— to develop new laboratory methods for chemotherapeutic trials in lepromatous leprosy ;

— to develop new chemotherapeutic agents active against *M. leprae ;*

— to plan the training of additional laboratory and clinical personnel recruited from leprosy endemic countries.

A screening committee in December 1976 reviewed applications for research grants and considered the methodology for the preparation of the standard protocol for clinical drug trials.

In 1977, the THELEP Scientific Working Group will finalize a standard chemotherapy trial protocol. Relevant applications for clinical drug trials will then be approved, and interrelated clinical trials will be sponsored and investigations undertaken to identify active principles in plants, e.g., hydnocarpus. With a standard protocol it will be possible to identify fairly rapidly the most appropriate therapeutic regimens using available drugs for leprosy control services.

6.1.3 Other collaborative research

The granting of technical and financial assistance to collaborating centres and institutions for various forms of research is a well established mechanism of the Organization. In 1976 it covered contractual agreements with thirty-seven research centres or principal investigators from 20 countries, apart from the IMMLEP and THELEP programmes.

The wide range of research studies and the number of centres involved are indicated below :

epidemiology of leprosy (6 centres); pathology (2); histological identification and classification of leprosy (1); immunology of leprosy (8); drug trials (1); research on *Myco. leprae* (20); systems analysis approach to leprosy control (1).

The most important of these studies are :

(*a*) *Operational/epidemiological studies*

These include 3 studies : the development of a simplified reporting system for leprosy programmes, allowing proper evaluation and comparison between countries, by the Department of Epidemiology, Catholic University of Louvain, Brussels ; in Burma, the use of multidisciplinary workers to effect integration of a specialized leprosy programme ; in Upper Volta to demonstrate the feasibility of a combined leprosy/tuberculosis project.

The Indian Council for Medical Research is co-sponsoring a further study of the possible prophylactic effect of BCG against leprosy and tuberculosis. In Mali, at the Institut Marchoux, Bamako, arrangements are being made between the Government, the OCCGE and WHO to undertake epidemiological studies in an area of 350,000 inhabitants.

(*b*) *Studies on myco. leprae*

Two WHO Collaborating Centres undertake studies on the biology and experimental transmission of *M. leprae,* standardize the techniques used, supply designated strains of *M. leprae* from animals and provide training in specialized techniques. Important studies on dapsone resistance are also carried out in cooperation with field control projects.

In addition, some 23 centres in 20 countries participate in the research on *M. leprae,* which is directed to three main areas :

— the cultivation of *M. leprae* in cell systems and in different cell-free semi-synthetic media, the metabolic requirements of the bacilli with a view to its growth *in vitro* ;

— the transmission of *M. leprae* to animals.

The most important advances in these areas are the development of the "nude" (congenitally athymic) mouse and the Lewis thymectomized rat which may have considerable practical value for antileprosy drug development and for monitoring chemotherapy.

(*c*) *Drug trials*

Several antileprosy drug trials have been completed recently at the Central Leprosy Teaching and Research Institute, Chingleput, India. They were mainly directed to studying the feasibility of intermittent dapsone therapy. The results of an open trial with clofazimine in the management of recurrent lepra reaction, a complication of certain forms of leprosy, were assessed.

(d) *Other studies*

In the chemoprophylaxis trial of leprosy, earlier studies at Chingleput, India, with oral dapsone reported a favourable protective effect of over 50%. A new study is in progress (1975-1980) using acedapsone (injectable every 75 days). If acedapsone is found effective, the reliability of its administration will have advantages over oral dapsone.

The IARC, Lyon, is studying the potential carcinogenicity of dapsone. The final conclusions are expected shortly.

During the period 1975-1977 some 68 publications and documents resulted from the WHO collaborative research in leprosy.

6.2 Regional programmes

The policy of increased research effort under the Special Programme for Research and Training in Tropical Diseases and the strengthening of the research capability in the affected countries is being implemented. In the American Region, a PAHO/WHO International Centre for Training and Research in Leprosy and Related Diseases, in Caracas, Venezuela, has already ensured the participation of national health personnel in trials of skin test antigens in Venezuela and elsewhere.

In October 1976, PAHO organized a Workshop on "Future Problems in the Microbiology of *M. Leprae*" in which some suggestions were made on ways of attacking the problem of *M. Leprae* cultivation, and questions related to the armadillo model were discussed.

A significant advance has been the establishment and convening of WHO Regional Advisory Committees on Medical Research (RACMR). Advisory Committees on Medical Research were established in AFRO, SEARO and WPRO during 1976, and in April 1977 SEARO held its third and WPRO its second session. AMRO which has regular sessions each year had its fifteenth session in 1976.

The South-East Asia Region has identified leprosy as one of the important areas of research following a regional consultative meeting on leprosy held in December 1975. In February 1977 a study group made recommendations on research studies in leprosy to be presented at the RACMR in April 1977.

The recommendations included investigations in the following areas :

(a) chemotherapy : development of simple criteria for identifying drug resistance, retrospective studies on its prevalence, comprehensive studies on relapses in lepromatous cases, drug trials ;

(b) chemoprophylaxis ;

(c) immunology : skin test antigens, development of serological methods for the diagnosis of leprosy ;

(d) development of alternative animal models ; and

(e) operational studies to improve present strategies.

The need for strengthening certain laboratories for experimental work at least with mouse models, was underlined.

7. Future programme development

7.1 Global strategy and approach

Based on the recommendations of the Expert Committee on Leprosy (1976), a reorientation in the approach to leprosy control is taking place, e.g., the programme formulation process as a part of country health programming is being developed as the most suitable method of assuring effective leprosy programme implementation. This approach entails close cooperation on all levels with health services and/or health care systems.

The nature of leprosy on the one hand, e.g., its slow evolution preceded by its long incubation periods and the equally long periods needed for treatment and follow-up of leprosy patients and for the surveillance of their house-hold contacts on the other hand, single out leprosy as an **a priori** disease for inclusion into permanent health care systems. Participation of health services in the planning stages, including manpower formation and information system needs for leprosy control activities, will be an important phase in future programme development.

7.2 Research

In addition to the TDR/IMMLEP and THELEP programmes, it has been recommended by the Scientific and Technical Review

Group of the TDR Programme that studies in the epidemiology of leprosy and research on cultivation of *Myco. leprae* be undertaken.

Relevant subjects for studies on epidemiology are mode of transmission, risk factors, environmental influences. Some of these studies would make use of tools developed by IMMLEP.

Attempts should be made to apply the recent advances in cellular physiology through a special programme aimed at achieving *in vitro* cultivation of *Myco. leprae*.

7.3 Regional and country level approach

The development of a programme oriented approach may be grouped together in the following main areas :

— programme formulation, including manpower and information system development, logistics, implementation and assessment ;

— research activities in association with TDR programmes.

Socio-economic situations in leprosy endemic countries differ widely from one country to another and even inside countries. A programme and target-oriented approach for leprosy control as part of health care activities needs to be modelled on the planned and existing stages of health care development.

Regional Offices draw advice from Regional expertise in leprosy control and research in the form of advisory groups on programme formulation, country level resource needs and research as exemplified by the Region of the Americas and the South-East Asia Region. Concurrently, there should be regional and country level acceptance of a global information system, so that an accurate identification of needs in each country can be made and coordinating services can seek to channel available resources appropriately.

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ILEP—A WORLDWIDE CO-ORDINATING STRUCTURE

P. VANDEN WIJNGAERT

ILEP—the International Federation of Anti-Leprosy Associations—was founded in Bern (Switzerland), September 1966, under chairmanship of Raoul Follereau, the founder of the World Leprosy Day.

ILEP brings together 24 national bodies concerned with helping leprosy sufferers. These bodies have their bases in 21 industrialized countries : in Europe, the 9 Common Market countries plus Finland, Norway, Spain, Sweden and Switzerland, outside Europe : Australia, Canada, Iran, Japan, New Zealand, South Africa and U.S.A. They are co-operating with 79 countries where leprosy is endemic : 36 countries in Africa, 21 countries in Asia, among which India, 17 countries in the Americas, 3 in Europe and 2 in Oceania.

Altogether, these 100 countries constitute a kind of international leprosy community where more than 2 million individual donors from industrialized countries are helping over a million of leprosy patients. More than 800 doctors heading mobile teams and treatment centres, with the help of 15.000 paramedical and administrative staff are participating in this worldwide campaign. Every year about 150.000 new leprosy patients are registered and about 50.000 patients are discharged in the 600 centres or projects sponsored by ILEP.

The total budget for the leprosy work undertaken by the Federation was about 25 million dollars US in 1976, of which 50% were expended in Asia, 40% in Africa, 7% for research programmes, the remainder in the Americas, Europe and Oceania.

In 1975, for example, in India, ILEP has supported 131 projects with 424.212 leprosy patients. The total expenditure for this support was of 2.600.000 dollars US.

The various aspects of leprosy work—as much medical and scientific as social and humanitarian—are to be found among ILEP's activities. Top priority is given to leprosy control, organized according to the methods settled by the World Health Organization, and thus based on early and systematic case-finding, treatment of every case detected, especially the active cases, and finally education of the public in matters of health and diseases, especially in leprosy. In 1975, ILEP was financing 156 leprosy control programmes in charge of more than 900000 leprosy patients. These leprosy control programmes include nation-wide leprosy control programmes, undertaken in co-operation with the Governments of 27 countries (20 in Africa, 4 in Asia and 3 in the Americas).

The second priority is scientific research : 34 projects were financed in 1975 with a total expenditure of 1.500.000 dollars US.

The third priority is training, with a total expenditure of more than one million dollars US for the support of 7 training centres amongst which 3 international institutions : ALERT in Addis Ababa (Ethiopia), Marchoux in Bamako (Mali) and Karigiri (Tamil Nadu) in India.

On the other hand, ILEP is paying a special attention to compassion towards leprosy sufferers and therefore has a long experience in rehabilitation activities, including physical, vocational, economic and social rehabilitation, especially in 24 technical co-operation programmes.

BUT WHAT IS REALLY ILEP ?

Along the years ILEP has developed into a co-ordinating body of organizations with operational activities, which thus became partners of a working community.

The basic principle that determines all the working relations within this community is an absolute respect for the individuality of each

partner in a spirit of frank and sincere friendship, born of adhesion to the same ideals. The role of ILEP, insofar as its co-ordinating function is concerned, consists in providing a framework that will ensure a harmonious equilibrium between the autonomy of the partner on the one hand and an encouragement of the maximum united efforts of the community on the other. Thus in the world-wide campaign against leprosy, ILEP itself presents a united front, but only its Member-Association actually do the work, ILEP may adopt a common policy, but each Member-Association decides on its own how this policy shall be applied. This type of organization, which is unique in this field, allows the individual Member-Associations to express their own genius in the most friendly kind of co-operation.

The functioning of ILEP is based, on the one hand, on the decentralization of operational activities and decision-making, and on the other on a strong centralization of information. Therefore, instead of centralizing funds as usually done in international federations of voluntary agencies, the Member-Organizations of ILEP have chosen to co-ordinate decision-making.

This is realized through a Co-ordinating Bureau, managing an information network and various kinds of Co-ordinating structures. Thus, the receipt of information, as full as possible, concerning centres and projects of the Member-Associations, and its dispatch to the Members, are assured. This network is kept supplied usually as the result of replies to standardized questionnaires (requests for financial assistance, and reports of activities) arriving from all aided centres, as well as from the budgets of all the Member-Associations which show the help accorded. In return, this information is collated into a series of documents, of which the most outstandingly useful are the Co-ordinate Budget and the Analytic and Financial Directory of the various leprosy projects. The Co-ordinate Budget keeps each Member-Association up-to-date concerning the centres and projects assisted financially in the course of the year, together with the amounts received from each partner. The Analytic and Financial Directory contains data available for the evaluation of the work of each centre or project, as well as of each country and continent, together with a global evaluation of the whole activities of ILEP. Thus each Member-Association is kept informed of the projects of all the other members, and the best possible opportunities for joint participation in such projects are offered, according to its available funds.

In a working community, information should logically result in action. Consequently, twice a year, in June and December, *Working Sessions* are organized, at which all Member-Associations participate in finalizing the budgets, projects and programmes. It is here that the many possibilities for joint action have their origin—action in the field, and combined action by a temporary partnership of several members. Two or three Members, for example, join together and agree to pool some of their funds for a certain period to finance a joint project, under the overall direction of one of them, called a Co-ordinator. This free exchange and pooling of funds, of resources and of responsibilities may be organized on the basis of a centre, a province, or even a whole country. It permits quite often the alliance of the experience of one Member with the know-how or financial resources of another Member.

It is easy to understand that a co-ordinating body like ILEP can, on the one hand, prevent wastages, duplication and overlaps, and dispersion of effort as much in financial matters as in field activities, and on the other hand, can result in the regrouping of the efforts of everybody by utilizing in the best way the talents of each in a combined effort on a world scale. It is only necessary to refer to the fact that a third of all the leprosy patients in the world now receiving treatment are actually being treated by Members of ILEP.

Joint action is impossible without a common policy, which, on the basis of a common motivation, constitutes the basis of all co-ordination.

It is a consultative body, the Medical Commission, that has assumed the task of drawing up guidelines for the leprosy campaign, which form the medical charter, as it were, of ILEP. The Commission is made up of eminent leprologists and of specialists in public health—all with long experience of tropical medicine. The Commission also examines projects submitted to it by Member-Associations. It makes practical recommendations on one or other point of general policy. It gives considered advice in the light of the most recent advances, medical and

scientific, concerning leprosy. It plays a major role in the selection of research projects financed by ILEP.

Working Groups have been set up recently to study specific problems, such as the training of staff in leprosy, health education in countries where leprosy is endemic, and the social rehabilitation of leprosy patients. The work of these groups will reinforce the general policy of ILEP and help to encourage all Member-Associations to adopt a common strategy.

The functioning of ILEP is thus characterized by a dynamic, composed of three strands—centralized information, joint action and a common policy—that determines how the funds raised by each Member-Organization shall be distributed. If the actual raising of the money is a difficult and thankless task, its judicious distribution involves responsibilities that are equally heavy. Despite its importance and its complexity, ILEP as an organization is not expensive. The cost of running it does not exceed a half per cent of the total sum distributed. Further than that, ILEP confers a new kind of image on the anti-leprosy associations, in the sense that it makes every dollar go a long way and adds precision, dynamism and the efficiency of a multinational undertaking to charity, generosity and solidarity towards the most deprived of our fellow-citizens.

TRENDS OF LEPROSY IN INDIA

P. KAPOOR

Dharmendra (13) in the First Silver Jubilee Conference Memorial Oration delivered at Baroda on the 10th April 1976 has stated "The National Leprosy Control Programme has now been in progress for a little over 20 years. Individual patients under treatment have no doubt being benefited as shown by decrease in deformity index and in frequency of plantar ulcers. However, it cannot be said with any degree of certainty as to what impact it has made in controlling the spread of the disease".

Vellut (31) in her paper has stated "To see the progress made in anti-leprosy work, one should sit at a leprosy out patients' table and simply look. The number of patients is high. Majority of them show minimum lesions; either residual shrinkeld patches or small well defined erythematous lesions, of recent origin. Very few patients present numerous erythematous lesions, positive for A.F.B. One or two would be on special treatment for complications. A good number of old patients for whom the attendance to a leprosy clinic has become a routine in life, for the last 10 to 15 years, with mutilations and trophic ulcers, come for a friendly chat, some for dressing and special shoes .... The possibilities of treating a large number of patients in a simple way has resulted in the launching of leprosy campaigns based on early detection and treatment .... Now after 25 years, it can be said that there is a definite progress, but a very slow progress in the field of control .... At an individual point of view, the results are exellent. A patient—lepromatous or non-lepromatous—who, at the first sign of disease, starts his treatment, and who takes it regularly under good medical supersision, is sure to be cured without deformity."

This sums up in short the progress and trend in leprosy in India. In order to understand and appreciate the changes that are seen in leprosy in India, it seems essential to know certain epidemiological features of leprosy and the working and progress of National Control Programme.

DEFINITION

Leprosy is a chronic communicable disease mainly affecting the nerves, the skin and mucosa. If it is not treated early and properly, it may lead to primary and secondary deformities. These deformities are the root cause of social stigma in leprosy (4).

TRANSMISSION

Though the exact mode of transmission of leprosy is not known, it is believed to spread mainly by infectious patients through contact with susceptible persons, both within and outside the house. (5, 11)

Nasal discharges from infectious patients are now being suspected as a major source for the spread of leprosy. (9, 10)

The spread of leprosy also depends on the immunological susceptibility or resistance of the persons coming in contact with leprosy patients. (6, 11)

HOST-FACTOR

The type of disease a patient may get depends on his immunological susceptibility or resistance. (6,11). Majority of early cases of leprosy heal spontaneously. Lara et al (22) has demonstrated that more than three fourth of all early cases in children heal spontaneously and completely. A person having very high resistance may not get the disease, or such a person may develop "an innocuous patch" which disappears spontaneously. When the resistance of the body is not very high, the person may get a localised form of leprosy called Tuberculoid type which is self healing by nature. (24). Some of these patients may, however, get deformities due to involvement of the trunk nerves, if they are not treated in time.

When there is little or no body resistance, a person may get a generalised form of leprosy called Lepromatous type. Such a patient is infectious and is mainly responsible for the spread of leprosy in the community.

Some persons have moderate resistance and they may get leprosy of Border-line type which is in between Tuberculoid and Lepromatous types of leprosy. Some of these patients may behave like lepromatous patients.

CASE DETECTION

Leprosy is manifested as a patch or patches on the skin. Large majority of leprosy patients begin with a patch or patches. These patients are easy to detect as the change in the skin is obvious.

Some patients may not have any patch, but have only slight lepromatous diffuse infiltration in the skin. (7), This diffuse infiltration is not easily seen and such patients are missed even when the people are conscious of the disease and the case detection work is satisfactory. Such patients are usually detected after a few years when the skin becomes thick, shiny or erythematous with small nodules, when eye-brows are lost and even signs of neural involvement develop. For the success of leprosy control, it is necessary to find ways and means to detect very early infectious cases.

The patients who have no or very little resistance, require a long time to be "disease arrested" and even after their being "disease arrested" they require maintenance treatment for a prolonged period. Such patients are usually not released from control and are continued on the list of active patients in almost all the centres.

DEFORMITIES

Deformities in leprosy are mainly due to the damage to the peripheral trunk nerves, resulting in sensory and motor paralysis of hands, feet, and eyes. Early deformities can be corrected or minimised by modern treatment, physiotherapy and surgery. (12, 25)

When the nerves are irreversibly damaged, the deformities persist, and it requires a patient with such deformities to be very careful about the use and care of his hands, feet and eyes. If the patient is not careful, secondary deformities which are preventable, may develop after injuries leading to gross mutilations. Treatment of such patients must include education of the patient regarding prevention of deformities. This is done in a few centres only. Deformed but "disease arrested" patients are always there in the community. They attract more attention then the non-deformed patients with active leprosy.

CONTROL PROGRAMME

Primary preventive methods of leprosy control are not available. Secondary prevention of leprosy control is based on case detection and treatment. (23).

Case detection work through surveys, contact examination and Health Education is done by the Para Medical Workers in the field. These Para Medical Workers, though allowed to detect and treat leprosy patients, are not allowed to release the patients from control even if the patients are "disease arrested". Medical officers and non-medical supervisors who are required to do this work are not in a position to assess all patients because of the excessive load of thousands of patients in their jurisdiction. Besides, Medical Officers usually take less than necessary interest in leprosy work. Therefore, even though the patients are "disease arrested", they remain on the list of active patients for a long time. This leads to apparent increase in the prevalence rate which is obviously not a real or true state.

COVERAGE

The coverage for leprosy control work has been very slow. Till the end of March 1976 only 212 million people were covered under National Leprosy Control Programme. (26).

NEWER TRENDS

With this back ground of some epidemiological features of leprosy and the functioning of the National Leprosy Control Programme, it may be possible to understand and appreciate the changes that have taken place in leprosy in India.

PAEVALENCE RATE

When the country became independent in 1947, there was no leprosy control as such. Patients were being detected, diagnosed and treated in a few special hospitals and clinics. There was no active case detection work. At that time, it was estimated that there were

10 lacs (1 million) leprosy patients in the country with a population of 36 crores (360 millions) (1951 Census), (13). Prevalence rate was 3 per thousand population. It may be noted that the data were based on a few surveys and the number of leprosy patients was grossly underestimated.

The present estimated number of patients in India is 32 lacs (3.2 million) (13) in an estimated population of 60 crores (600 millions) giving a prevalence rate of 5 per thousand population.

Estimate of 32 lacs of patients is based on the intensive work done in the country from 1955 on-wards mainly in the endemic and hyper-endemic areas. The author estimates that about 10% of the patients are registered at more than one place. The reasons for such multiple registration are, (i) ever increasing number of leprosy centres: bringing the place of treatment near the houses of the patients so that they leave their earlier distant clinics and join the new ones, (ii) increased mobility of patients, (iii) patients losing faith in one clinic, register at other places etc. In addition, over the years, the disease arrested patients are not removed from the list of active patients but new patients are being added. Thus there is cumulation of numbers. (13). In all the centres in the country where the cases of such patients have been reviewed, the prevalence rate has been reduced by 30 to 72%. (1, 34).

In a recent study in Maharashtra (19, 35) similar has been the experience.

Jacob Thomas et al (16) however reports an increase in the prevalence rate in a centre in Bihar, although there has been a marked decline in lepromatous rate and ratio.

If due discount is given for the above factors, it will be realised that the true prevalence of leprosy in India would be actually much less. The author estimates that there are about 18 to 20 lacs (1.8 to 2 millions) of leprosy patients in the country giving a prevalence rate of about 3 per thousand. This estimate is considered to be more realistic.

INCIDENCE OF LEPROSY

No National studies have been undertaken to study the incidence of leprosy in various parts of the country. A few studies that have been reported are from special centres. Rao (27) has reported a decline of 50 to 58% in incidence rate. Das (8), Ekambaram (14), Chatterjee (3) and ELEP Leprosy Control Centre, Dharmapuri (2) have also reported a similar decline in the incidence rates. Noordeen (24) however, does not report any decline in the incidence.

NEW CASE DETECTION RATE

No generalisation is possible on the basis of these few studies in special centres. Some idea may be available from the new cases detected in the Leprosy Control Units working all over the country. Most of the Leprosy Control Units are now recording less number of new patients as compared to the past. These show that there is a definite decline in new case detection rate. (18, 19, 28) In all such centres, the decline is between 40 and 50% during the first 10 to 15 years of work. After this, there is no decline seen. Vellut (30, 31) however, reports that the number of patients registered every year since 1963 has remained the same. The author believes that even though the new cases registered have remained the same, but in view of the increasing population, the rate per thousand population would be less now than in the past.

Wardekar (36) believes that a plateau of decline is reached in about 10 to 15 years and it might be possible that we have reached this plateau in the areas where the work is being done for 10 or more years.

This shows that transmission of leprosy has not been interrupted, possibly for the reasons that there are undetected early lepromatous cases in the community and/or the possibility of so called non-infectious patients being infectious to a certain extent or at a certain period in the natural history of the disease (5, 11).

The other major factor seems, as is the experience of all workers, to be that 20 to 30% of the infectious patients do not take any treatment and the drop out rate of patients from the treatment is equally high.

DEFORMITY RATE

The greatest change seen amongst new leprosy patients is that they are mostly not deformed. The deformity rate amongst new patients has come down from 30-40% to less than 10% in most centres, and less than 5% in some centres. (2, 17, 18, 30, 31). Child leprosy patients with deformity are not usually seen these days. (20).

Deformity rate amongst patients detected by surveys is considerably reduced after the second survey. The deformity rate in patients who report voluntarily is comparatively high (20, 30) but is still much less than what it used to be in the past. It varies between 10 to 20% in various places. This shows that much more is required to motivate the people to seek early diagnosis voluntarily. Most of the deformities that are seen these days are early deformities which may be corrected with treatment including physiotherapy and surgery. Vimla Dermatological centre working in a northern suburb of Bombay has however not registered a single new deformed case out of 700 new cases registered between April 1976 and March 1977 (33). Ganapati (15) has reported 12 cases with deformity out of 189 in a suburb of Bombay from October 1976 to May 1977.

New patients with neuropathic ulcers are also very few. Not more than 5% of the new patients have neuropathic ulcers. (2).

LEPROMATOUS LEPROSY

Even though it is difficult to detect early lepromatous leprosy, the deformity rate in lepromatous patients is also considerably reduced. (2). It is now between 15 and 20 as against more than 50% in the past. New patients with big nodules and leonine face are seen only rarely. (31, 32).

There is a decline of lepromatous rate amongst new patients to the extent of about 50 to 60%. (18, 31) Children with lepromatous type of leprosy are only occasionally seen, because of early detection. (20).

PUBLIC CONSCIOUSNESS AND ATTITUDE TOWARDS LEPROSY

People have become leprosy conscious. They are conscious about the early signs of leprosy, availablity of treatment and curability of the disease. This is evident from the fact that 40 to 50% of new patients have only one lesion. (15, 17, 20, 31) About 35 to 60% of the new patients report voluntarily. (15, 20, 28, 31) The stigma of leprosy that was there in the past has been much reduced. (8, 21, 29) Patients stay in their homes and take treatment. The patients are rarely thrown out of the house/village unless the economic condition of the patients/family is very poor. But the patients who are already out of the family/village still find it very difficult to be rehabilitated in the family/village. The people are conscious about leprosy but they are yet not fully motivated for taking regular and continuous treatment. Percentage of the patients taking treatment and those who drop out of treatment, has remained the same. Patients refusing to take treatment and dropping out of treatment, are the major problems which require to be studied by a competent team comprising of social, behavioural and medical scientists.

BEGGARS SUFFERING FROM LEPROSY AND SELF-MADE COLONIES OF LEPROSY BEGGARS

No studies are available on this aspect of the problem. One may not be surprised if there is no change in their number (percent to the total population). This does not reflect on the National Leprosy Control Programme, as the problem is more socio-economic. The author has seen that most of the leprosy beggar colonies are well-organised by the patients themselves and treatment facilities are made available to them by Government, Municipalities or Voluntary Institutions there. The regularity of attendence for treatment in such colonies is usually higher than among the general patients. The disease in many of the leprosy beggars is inactive, though almost all of them are having deformities and mutilations.

CONCLUSION

In conclusion, it may be stated that although the interception in the transmission of leprosy has been limited in extent, there seems to be no real increase in prevalence of leprosy in India. Any apparent increase is due to one or a combination of factors like: (a) cumulation of cases in the control areas because of failure to remove disease-arrested or cured cases; (b) more efficient case detection with successive surveys; (c) double enumeration of cases in neighbouring clinics; (d) addition to the existing number, of cases from newly opened control units in virgin or hitherto uncovered areas. On the contrary the overall picture seems to be changing slowly for the better. The patients are detected early and saved from getting deformities which is the root cause of the stigma & fear. Leprosy consciousness in the community has increased and there is less of stigma and harrassment of leprosy patients. Both lepromatous and deformity rates have been considerably reduced. Any increase reported from any area is almost wholly attributable to non-

lepromatous cases. This last observation holds true to some extent even in newer areas brought under control coverage. The general complaint of leprologists of the rarity of good lepromatous nodules to prepare his lepromin from, is noteworthy in this context. These observations need not however generate undue optimism and a great deal remains to be done. There is particularly a great and immediate need for the involvement of general medical officers and practitioners in the leprosy control work and also for scientific multi-disciplinary studies to find out the reasons for drop out from treatment even in situations where the result of treatment is obvious to the patient.

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LEPROSY IN THE WORLD

WHAT IS THE PRESENT SITUATION? STATIC OR CHANGING?

S G BROWNE

The short answer to the question is, it is impossible to say. The same considerations hold in most countries for all transmissible diseases, especially those that are chronic. Notifications of acute communicable diseases, like poliomyelitis and typhoid, may be reasonably complete where medical services are adequate, but a disease like leprosy tends to be under-reported and under-notified, even in the best of circles. Leprosy shares with other diseases this incubus of being under-reported in areas where medical services are scanty or even non-existent. The reasons are not far to seek: the difficulties of diagnosis by reason of the extremely varied clinical picture; the absence of the pain that would in the case of many other diseases bring the patient to the doctor or paramedical worker; the insidiously progressive nature of the physical signs of leprosy infection; and, above all, the social stigma attaching to the condition, which makes sufferers and their families hide their "guilty" secret for as long as they can.

Leprosy is, in most countries, still a rural rather than an urban disease—since the young and the healthy gravitate to the towns, and the risks of transmission are generally less in the towns; hence, the medically deprived and under-doctored rural areas of the developing countries have an unduly high proportion of leprosy sufferers, often unsuspected, unrecognised, and unknown to the medical authorities.

The statement that leprosy is a rural rather than an urban disease, needs to be modified today in the case of a country like India. The selective migration to the towns is now of families rather than of healthy young single males seeking work, and families tend to take leprosy with them. Thus, Bombay, Madras and Calcutta all have their considerable leprosy problem, and the growing towns all over India are having to cope with an influx of leprosy sufferers, by no means all of them beggars.

Of course, there are some compensating factors: in areas where effective antileprosy control measures have been in operation for long periods (as in French West Africa), the incidence of new cases may show considerable reductions. Owing, however, to the reluctance of medical auxiliaries to discharge registered patients—and the reluctance of the patients themselves to be discharged—after clinical quiescence has been attained, these ex-leprosy patients continue to swell the numbers of those suffering from supposedly "active" disease.

Another very important, and interesting, factor is the proportion of cases of self-healing leprosy in the community. In areas where whole-population surveys can be regularly undertaken, as in Polambakkam and similarly investigated areas, the total numbers of patients with recognizable leprosy lesions may show rather frightening dimensions—frightening, that is, unless it is realized that with an increasingly adequate medical coverage, the number of cases of early "indeterminate" leprosy, transient and self-healing (like the primary affect in pulmonary tuberculosis), may represent a not inconsiderable proportion of the total number registered.

A factor that cannot be ignored in the consideration of global trends in the leprosy endemic is the fact of population growth. While the growth rates in Western countries are tending to slow down and stabilize, those in the countries of the Third World are still showing annual increases of up to 4.5 per cent.

And it is precisely in these countries that leprosy—among other diseases like tuberculosis, returning malaria, and water-borne and pulmonary diseases—still poses a considerable health problem. There are more people to catch leprosy. And catch it they do.

A curious feature of the leprosy endemic in India and in other countries is the patchy nature of the prevalence rates. Thus, Tamil Nadu, West Bengal and Orissa have high prevalence rates, but within these States the prevalence is by no means uniform. Then Haryana and the north-west in general have low prevalence rates, but nevertheless there are pockets of much higher prevalence. In some areas, those afflicted tend to congregate in certain villages, or in certain areas in the bigger towns, where, untreated, they constitute a source of hyperendemic infection. Racial factors determining resistance, perhaps coupled (fortuitously or not) with degrees of cutaneous pigmentation, may be at work here.

The overridingly important factors are the presence of leprosy sufferers shedding viable bacilli from the nasal mucosa, and susceptible contacts within the range of the infective droplets. Thus domestic overcrowding, given the existence of an infective index case, would be a most important factor in the persistence of an endemic focus.

The pocketing of clusters of susceptible subjects can be seen, for instance, in the communities in Venezuela of German extraction, in which leprosy continues to be highly prevalent. On the other hand, the third—and fourth-generation descendants of the leprous Scandinavian immigrants into the Middle West States of USA are today completely free from leprosy infection. Pockets of leprosy can be traced in a country like Colombia, where the Spanish soldiers settled and have left a trail of leprosy infection. The higher susceptibility to leprosy of the lighter-skinned descendants of the Spanish is a well-attested fact of observation. In Asia, it is noteworthy that wherever the troops of Chenghis Khan bivouacked, leprosy is now present and the population bears traces of mongoloid features.

Estimates, of course, from government sources or from voluntary agencies, may vary widely, dependent on available data, presuppositions, and perhaps prejudices. It is still rather "shameful" to have to admit that one's country has a leprosy problem, and still more shameful if the problem is not being reduced in size and importance. Nevertheless, and not-withstanding the absence of statistics from several countries where leprosy must constitute a sizeable problem (such as mainland China), and the lack of accurate statistics from several other countries, it is possible to hazard some reasonable guesses about the trend of leprosy in the world today.

The first bleak fact is that the size of the problem is not diminishing, in absolute terms. The best official figures of the World Health Organization, based for the most part on government returns, suggest that the total number of leprosy sufferers in the reporting countries is 11.2 millions. The distribution, country by country, has remained virtually unchanged since quasi-accurate statistics first became available. The total number of cases formerly showed an increase consequent on the more accurate reporting and the increased coverage of medical services. Thus, in India in the year 1874 the official estimated number of leprosy sufferers was 93,231. Now, the official estimate is 3.2 million. Whole areas in which leprosy is highly endemic have been opened up of recent years to medical service and surveys.

Some few countries show a real diminution in the prevalence of leprosy. In general, these are the countries where good medical services and adequate finance are available. Thus, Japan can point to an apparent success of its policy of humanely-enforced segregation, with a reduction by two-thirds of its leprosy population in 30 years. The old are dying out, and new accessions to the leprosy totals (apart from new medical areas, like Okinawa), are few and manageable. South Africa is another example of a similar trend. And, in the more distant past, the considerable leprosy endemic in the countries of north-western Europe (particularly Scandinavia) has diminished to vanishing point. The situation, however, in Southern Europe remains practically static —mainly because of the non-recognition of early leprosy by the average medical practitioner, despite the general availability of adequate medical services: this situation holds for Portugal, Spain, Italy, Greece, Turkey and Southern Russia, not forgetting the Mediterranean islands of Cyprus and Malta.

In the countries of the Near East, and North Africa, the situation is far from clear and far from complete. Leprosy is endemic in the whole of North Africa (Morocco, Tunis, Algiers, Libya, Egypt, Sudan), and in the lands of the near East—but although the prevalence rates are supposed to be low, there are pockets of high rates of considerable size and importance. To judge from the advanced clinical state of patients examined soon after they have presented themselves for the first time—always a good indication of awareness of leprosy by the public and the medical profession—the leprosy situation generally is more serious than the authorities care to admit. This would be the situation in countries like Iran and Afghanistan. When leprosy is not suspected, or medically diagnosed, until gross deformity has occurred, or advanced leonine facies has appeared—then the gravity and size of the endemic may remain quite unknown.

Subsaharan Africa represents a region of very high leprosy prevalence, very low lepromatous/tuberculoid ratio, and a mixture of continuing effective leprosy control programmes and a disruption of rural medical services. The two countries that have very serious and large leprosy problems—Nigeria and Zaire—have for various reasons not succeeded in facing the situation realistically.

In the French-orientated countries of West Africa (the former French colonies), the maintenance (although modified) of the old service (largely dependent on French military medical personnel for its inspiration) combating the major endemic diseases, seems to have borne fruit in the published reduction in both prevalence rates by up to three-quarters, and incidence rates by four-fifths or even more. Although these average figures conceal fairly wide divergences reflecting the success and activities of the organization, the fact remains that in vast areas of high leprosy prevalence—albeit of low lepromatous/tuberculoid ratio—significant results have accrued from a consistently applied strategy.

In South and Central America, the leprosy situation is probably static, within extremes represented by (continental) Chile (where leprosy is apparently non-existent) to considerable pockets in Brazil, Venezuela and Argentina—and the other countries often associated historically with the irruption of Iberian invaders.

In Australia, the leprosy situation among the aboriginal "walk-abouts" (of enormous interest epidemiologically) is probably improving, thanks to a good medical service. In New Zealand, leprosy is in the main a disease imported from the islands of the South Pacific, which themselves have a sizeable problem.

Several factors have of recent years complicated and modified the leprosy endemic. The most important of these factors is movement of populations—from the villages to the towns in countries of the Third World, from southern Europe northwards, from the developing countries to the industrialized, and from a country like Italy to Canada, from Puerto Rico and Mexico to the USA, and from Indonesia and Surinam to Holland. Although the influx of immigrants from leprosy endemic areas (like India, Pakistan, Nigeria, the West Indies) to Great Britain has been of large dimensions, and although the great majority of leprosy notifications is, as would be expected, among the immigrant population, yet cases of indigenously contracted leprosy in the industrialized countries of Europe are extremely rare. Two or three centuries ago, the extent of the leprosy endemic in countries of north-western Europe was, even on conservative estimates, quite considerable. It has now virtually disappeared—and the precise reason or reasons for its disappearance are not known.

Mainland China is an unknown quantity as far as leprosy is concerned, since no figures have been forthcoming recently. Thirty years ago it is known that leprosy was widespread in that land, and there is no reason to suppose that in China the disease has proved more amenable to accepted control measures than elsewhere. Certainly, in countries with similar ethnic populations, like Korea, Taiwan and Thailand, the size of the leprosy problems seems not to have changed much during the past few decades.

Another new factor likely to become increasingly important during the next few years is the emergence in many countries of leprosy bacilli resistant to the sulphones. This fact will affect the prevalence of leprosy in several ways—not only the actual presence of sulphone resistant disease, primary and secondary, but also the attitudes to leprosy and its treatment that will be engendered in the community itself, in governments and in voluntary agencies concerned with leprosy. Leprosy will be seen to constitute a more

intractable and costly problem than has been hitherto realized.

Coupled with the grim prospect of the emergence on a world scale of sulphone-resistant leprosy bacilli, comes the disquieting news that some leprosy bacilli—"persisters", they are called—may remain viable but dormant despite the regular taking of anti-leprotic drugs in adequate amounts. These non-metabolizing dormant bacilli, ready to begin multiplying again when conditions are propitious, will account for the persistence of the leprosy endemic, and perhaps its sudden and unexpected flare-up in circumstances where leprosy control was believed to have been achieved.

As if that was not enough in the way of threatening prospect, there is evidence accumulating that some "wild strains" of the leprosy bacillus, that is organisms that are found in newly-diagnosed patients, are not as susceptible to the sulphones as was formerly the case. That is, the threshold of sensitivity to the main drug used in leprosy treatment is higher than it was; higher doses of dapsone are required to prevent the multiplication of the organism.

Influence of BCG

It is difficult to assess the influence on the incidence of leprosy of widespread vaccination of infants and young children with BCG. The complex and equivocal results of the three major investigations (in Uganda, Burma, and Papua New Guinea) might suggest that in situations epidemiologically comparable to that obtaining in Uganda, a reduction in the incidence of new leprosy infections in children might be expected to follow widespread vaccination with BCG. In the absence of expert oversight and critical evaluation, however, it is to be regretted that the effect of BCG vaccination cannot yet be ascertained precisely; the high hopes elicited at first cannot unfortunately be realized, and reduction in the incidence rates of leprosy must still be dependent on the reduction of the reservoir of infectious patients and on the opportunities for the infection contact.

The possible effect of the use of prophylactic dapsone on a wide scale, also cannot be assessed—apart from the financial and administrative (and immunological) objections to this procedure maintained for a long time in a healthy population exposed to leprosy.

To sum up—notwithstanding the facts that a tremendous effort has of recent years gone into the treatment of some three million cases of leprosy at any one time, and that probably two million cases have been discharged "disease arrested", the sum total of those suffering from leprosy today has shown no appreciable change in the world as a whole. This is a sobering thought. A drug is now in existence (rifampicin) that will in a few days render non-contagious those suffering from contagious forms of leprosy: if this drug could be given on a wide enough scale to all persons needing it, the reservoir of infection would decline dramatically.

Notwithstanding the sombre nature of these reflections on the present state of leprosy in the world, it is still true to say that we possess the means and the knowledge to control the scourage, provided that we use the means and apply the knowledge with sufficient determination and on a sufficiently wide scale.

EPIDEMIOLOGY OF LEPROSY; CURRENT VIEWS, CONCEPTS AND PROBLEMS

RICARDO S. GUINTO

Etiology, Sources of Infection and Infectiousness

The specific agent. We can now say that the causative agent of leprosy is *M. leprae.* The fact that the characteristic lesions of lepromatous leprosy are associated with tremendous numbers of *M. leprae* does not, of course, constitute complete proof of etiology. Swine fever, for example is caused by a virus but is accompanied by secondary invasion with Salmonella cholerae suis.

Animal models now provide definite experimental support for *M. leprae* as the causative organism. First reported by Shepard in 1960 (81, 84), the characteristic limited multiplication of *M. leprae* in mouse footpads has become an established and consistently reproducible procedure for therapeutic and other important laboratory studies (76). In fact, the specific growth pattern of *M. leprae* in mouse footpads, combined with uncultivability in artificial media, is now used as a method of identifying unknown mycobacteria as *M. leprae* or not (76).

Rees (73, 74) reported a more disseminated though still atypical *M. leprae* infection in mice immunologically depressed by thymectomy and x-ray irradiation. More recently, Kirchheimer and Storrs (48) reported that one nine-banded armadillo, out of 40 inoculated at various dates, had so far developed a disseminated infection closely resembling human lepromatous leprosy. Subsequently developing armadillo infections have since been shown by a number of authors (87) to be clinically and histopathologically very similar to human lepromatous leprosy. A new paper by Storrs et al (88) reports that no less than 8 out of 20 armadillos or 40% developed severe lepromatous leprosy 3 to 3.5 years after inoculation with *M. leprae,* and that about 1 kilogram of lepromas containing an estimated 15 to 20 grams of pure *M. leprae* were obtainable from these 8 infected animals. The authors emphasized the great potential of the armadillo as an animal model much needed for microbiological, immunopathological, therapeutical and epidemiological (preventive) leprosy research.

Mitsuda and Hayashi (44) recognized as far back as 1933 that lepromatous patients were anergic to lepromin but reactive to suspensions of mycobacteria other than *M. leprae;* and furthermore, that this unique immunological finding could be used as a means of identifying mycobacterial isolates as *M. leprae* or some other organism. This method of immunological identification was used successfully by Shepard and Guinto (82) in 1963. A lepromin prepared from infected mouse footpads gave negative Mitsuda reactions in lepromatous patients and positive reactions in tuberculoid patients which were almost identical to the reactions of the same patients to regular lepromin. In a study recently completed in Cebu (43) 21 lepromatous patients gave completely negative Mitsuda reactions to human lepromin, to armadillo lepromin, and to mouse footpad lepromin; but gave definitely positive Mitsuda reactions (i.e., clinically and histopathologically) to a similarly prepared suspension of *M. lepraemurium* from infected mice. In marked contrast, as expected, 26 tuberculoid patients gave positive Mitsuda reactions to all 4 antigens. As with a similar report from Zaire by Meyers et al (59), the above finding provides important immunological confirmation that infection with *M. leprae* indeed causes lepromatous leprosy, also not in all, as in human leprosy, but in about 40% of the inoculated armadillos.

Sources of infection. The accepted view is that human cases discharging *M. leprae* constitute the only sources of infection, whether lepromatous, non-lepromatous and perhaps even subclinical. No new evidence disputes this long held view. Lepromatous

patients are known to discharge millions of *M. leprae* from skin lesions, presumably even without ulceration according to Muir and Chatterjee (63) and Weiner (92), and very especially though nasal secretions (69, 16). The viability or infectiousness of *M. leprae* from nasal discharges has been demonstrated by positive inoculation into mouse footpads (16). There is no question with respect to the similar viability of *M. leprae* obtained from skin lesions of untreated lepromatous patients.

Association between "heaviness" of infection with M. leprae and incidence. The well-known fact that contact can be traced far more frequently to lepromatous than to tuberculoid primary cases was of course recognized long ago by Hansen, Rogers and Muir, and many other distinguished leprologists. Rogers and Muir (80), for example, reported that of 113 cases in which the probable source could be traced, only 5.3% of these sources were tuberculoid, while the rest were lepromatous. Epidemiologic studies by Lowe and Dharmendra (54), Lampe and Boenjamin (50) and others have likewise been consistent in finding the highest incidence among those living in close contact with lepromatous cases.

TABLE 1

COMPARATIVE AVERAGE ANNUAL ATTACK RATES FOR PERSONS EXPOSED AND NOT EXPOSED IN THE HOUSEHOLD TO LEPROMATOUS OR NON-LEPROMATOUS LEPROSY. CORDOVA AND TALISAY, CEBU, PHILIPPINES

Study	Attack rate per 1000 person-years		
	With household exposure		Without known household exposure
	To lepromatous primary cases	To non-lepromatous primary cases	
1st study: 1935 (retrospective)	6.2	1.6	0.8
2nd study: 1935-1950 (observation)	4.4	1.0	0.8

The cebu studies of the Leonard Wood Memorial and the Philippine Department of Health were perhaps more precise than other epidemiological studies in measuring the relative risks of household exposure to lepromatous (including Borderline) leprosy as compared to the tuberculoid type. As summarized in Table 1, in an earlier retrospective pre-survey study (20), it was found that when the primary case was lepromatous the attack rate for contacts was equivalent to 6.2 cases of leprosy per 1000 persons per year. When the primary case was tuberculoid, however, the incidence was 1.6/1000/year, while the corresponding rate for persons without known household contact was only 0.8/1000/year. Thus the estimated risk of contracting leprosy was 4 times higher in close contacts of lepromatous cases than in those of tuberculoid cases, and nearly 8 times higher than in noncontacts.

The same population was followed up for 15 years in a subsequent study (34), which this time showed a slightly lower attack rate of 4.4/1000/year for contacts of lepromatous cases, compared to 1.0/1000/year for contacts of tuberculoid cases and again 0.8/1000/year for noncontacts. The risk of contracting leprosy in this observational study was again 4 times higher for exposure to lepromatous as compared to tuberculoid leprosy. The incidence among contacts of tuberculoid cases, however, was only 1¼ times that among noncontacts. It should be noted from the dates in Table 1 that these attack rates were obtained in the population of Cordova and Talisay, Cebu, before the advent of sulfone therapy and of BCG vaccination against tuberculosis.

More recent studies have confirmed the above findings. In a recent follow-up of about 14,000 contacts in the Chingleput District of South India, the attack rate for those exposed to the lepromatous type of leprosy was 3 times higher than for those exposed to the nonlepromatous type.

Infectivity of tuberculoid leprosy. There is no reason to doubt the much lower infectiousness of tuberculoid as against lepromatous leprosy. There are questions, however, regarding the continuing spread of leprosy in hyperendemic areas where 90% or more of all known cases are tuberculoid. Davison in South Africa (17) and Kinnear Brown in Uganda (47) among others strongly object to the view held by some that only

lepromatous cases are infectious. These authors believe that lepromatous cases are too few and scattered to account for the vary high prevalence of leprosy in much of Africa, and that of necessity, tuberculoid cases must be mainly responsible for the spread of the disease.

Smears from tuberculoid patients are generally negative, although after careful search and special methods of examination, small numbers of *M. leprae* are often demonstrable. The bacilli, if present, are likely to be deep in the dermis or within nerves and unable to escape, making such cases "closed" or relatively uninfective. On the other hand, tuberculoid cases are liable to undergo periods of clinical exacerbation, during which they become bacteriologically positive and undoubtedly infectious. The part played by tuberculoid cases in the spread of the disease may thus depend not only on their relative prevalence, but also on the frequency, duration and severity of these exacerbations which must surely make them infectious.

There are wide geographic and racial differences in the lepromatous-tuberculoid ratio, and also in the clinical manifestations of the tuberculoid type of leprosy. In Ghana, for example, the majority of patients admitted to leprosaria are classified as tuberculoid, but with painful neuritis and other "reactional" tuberculoid lesions as the reasons for admission. In the Philippines, on the other hand, most institutionalized patients are lepromatous and many tuberculoid cases have minimal or solitary lesions which heal even without treatment, and among those undergoing clinical reaction, painful neuritis is only rarely observed. Climatic and other environmental influences may cause more clinical exacerbations among tuberculoid cases in some countries than in others, so that comparative regional studies of such occurrences are obviously needed. Some consideration might even be given to the possible existence of strain differences in *M. leprae* with varying pathogenicities.

A theoretical and simplified explanation may be offered for the continued high prevalence in places where 90% or more cases are tuberculoid and only 10% are lepromatous. Assuming a random distribution of the cases, we may expect 90% of the population to be exposed to tuberculoid primary cases and the remaining 10% to the lepromatous primary cases. If the risk of contracting leprosy for contacts in Cebu were applied to the above population (i.e., 1.6/1000/year for exposure to tuberculoid vs. 6.2/1000/year for esposure to lepromatous or about 1:4), the following attack rates would prevail: $(1.6/1000 \times 0.90) + (6.2/1000 \times 0.10 = \frac{1.44 + 0.62}{1000}$ or 2.06 cases per 1000 persons per year, notably with tuberculoid cases contributing $1.44/2.01 \times 100$ or 70%, the greater share of the infections.

Further assuming an average duration of 5 years for each new leprosy case, an annual incidence of 2.06 would cumulate to a prevalence of 10.3/1000 after 5 years; similarly, an average duration of 10 years would add up to a prevalence of 20.6/1000 after 10 years. The hyperendemicity may thus be maintained if lepromatous and tuberculoid cases in Africa were at least as infectious as in the Philippines, and especially if tuberculoid cases in Africa were more infectious than those in Cebu. Because of greater total exposure, the less infectious but far more numerous tuberculoid cases would be responsible for more infections than the lepromatous cases. Tuberculoid cases are of course highly predominant in all areas of the world where the disease is hyperendemic.

Inapparent or undiagnosed "open cases." It is well known that even in highly endemic areas, contact to a known case of leprosy cannot be established in the majority of instances. Much of this is no doubt attributable to the long incubation period and slow development of the disease, so that years may pass between infection and detection. Poor case-finding and the general tendency to hide leprosy are also contributory factors. If known leprosy cases constitute the sole source of infection, careful investigation of leprosy in young children would be expected to disclose a positive history of contact in most of them. Such a finding has never been quite realized. Out of 19 cases developing in children under 5 years of age, Guinto et al (34) found that contact could be traced to an antecedent case in only 10 instances.

All leprologists have seen occasional bacterio-positive cases of leprosy with lesions so mild and inconspicuous as to escape detection for long periods. Such "missed" primary cases, who could have died, moved away or even undergone spontaneous healing before discovery of their secondary cases, may provide a plausible explanation for some untraced infections. Although often severe, lepromatous lesions may range all the way

down to almost clinically undetectable cases. Muir was to all intents describing what might be termed "incubatory" carriers of leprosy when he stated in his book that "in many lepromatous cases I should say probably in the majority of them when the skin is dark, leprosy bacilli can be found in the skin, often in large numbers, before, there are any visible clinical signs".

The question of asymptomatic leprosy infections. As was said, contact sources are untraceable in most leprosy cases. Furthermore, although attack rates are 4 or more times higher in contacts than among noncontacts, the former contribute only about 1/3 of the total cases of leprosy in the community. Consideration might thus be given to the possibility that leprosy may also be spread by "healthy" carriers.

Evidence of a possible carrier state in leprosy was first advanced by the Bombay group led by Figueredo and Desai, and by Khanolkar (18, 30); and later by the Johns Hopkins group headed by Taylor (89). Desai (18) reported finding acidfast bacilli (AFB) in no less than 610 or 48% or 1266 apparently healthy contacts (whether of tuberculoid or lepromatous primary cases), and presumably only in 31 or 4% of 756 presumed noncontacts. AFB were found in the earlobes, back, forearms or thighs of these apparently healthy contacts, virtually implying hematogenous dissemination of *M. leprae* (?) in these suspected subclinical infections.

Taylor et al (89) presented more believable evidence of asymptomatic leprosy in a careful study of family contacts from Purulia, Bengal as compared to controls from the Punjab. AFB were found in skin biopsied from the ears of 24 or 20% of 121 family contacts of lepromatous cases, but only in 2 or 2.5% of 80 contacts of tuberculoid cases, while no AFB were found in any of the 50 controls from Punjab, where there had been no known leprosy for many years. All examinations for AFB were done blindly. The proportions reported by the Johns Hopkins group would be logically expected if the AFB in the ear biopsies were actually *M. leprae*. The authors therefore deduced that they had confirmed the Bombay findings and demonstrated the existence of asymptomatic leprosy infections, although without as yet any proof that these could spread the disease.

The reports of a possible carrier state in leprosy are important because of their epidemiological implication. Dharmendra, Sagher and others (24) have also found rare AFB, but in far fewer numbers of healthy contacts. The prevailing opinion is not in favour of a carrier state in leprosy, not until the AFB in these individuals are positively identified as *M. leprae* and not merely saprophytes. It might be possible to obtain sufficient numbers of AFB from these persons for identification by Shepard's mouse footpad inoculation technique.

A new immunological concept of subclinical infection. There has been no specific test for detecting past or present infection with *M. leprae* (such as the tuberculin test in tuberculosis), and there is a great need for a means of identifying individuals actually or previously infected but without clinical signs, including possible carriers. According to Godal, Myrvang et al (32, 64, 33), in leprosy as in most infectious disease, only a certain proportion of those exposed actually develop clinical disease, while the rest mount a successful immune response before it has time to cause disease; and these individuals should be considered to have gone through a stage of subclinical infection.

Godal and Myrvang (32, 64, 33) report that two *in vitro* tests currently used for monitoring T-lymphocyte function—(1) the Lymphocyte Transformation Test or LTT, and (2) the Leucocyte Migration Inhibition Test or LMIT—are now both sufficiently specific for detecting immune responses elicited by *M. leprae* alone, if unautoclaved *M. leprae* is used as the antigen in these tests. A total of 71/122 or 58% of medical attendants working closely with leprosy patients in Ethiopia responded positively (with greater than 2% transformation) to LTT, and 37/52 or 71% of them responded positively (with greater than 80% migration) to LMIT. Similarly, 18/29 or 62% of contacts of tuberculoid cases gave positive LTT reactions, compared to 24/59 or 41% of contacts of lepromatous cases; only 12 household contacts were examined by LMIT and 6 or 50% gave positive reactions. In contrast, none of 26 individuals from nonendemic areas responded to LTT and all of the 10 tested with LMIT gave negative reactions. The authors consider the above results with LTT and LMIT as new evidence to the effect that subclinical infection occurs frequently in leprosy. Leprosy is made to appear much more contagious than indicated by known prevalence and incidence rates. In particular, tuberculoid leprosy is made to appear highly in-

fectious. The numbers of contacts and controls tested with LTT and LMIT by the Godal-Myrvang procedure are relatively small. Because of the implication to epidemiology, their findings certainly require further investigation and confirmation by others.

Infectivity of solid and nonsolid M. leprae. Two recent laboratory findings are important from an epidemiological standpoint: (1) *M. leprae* which appear beaded or nonsolidly stained by the Ziehl-Neelsen method are considered *dead* (noninfective), primarily because they fail to multiply in mouse footpads; and (2) solidly stained *M. leprae* are considered *viable* (infective), because they multiply consistently in mouse footpads (58). As a result, two laboratory criteria have been adopted for measuring the infectiousness of patients who are still bacteriologically positive: (1) the Morphologic Index (MI) or percentage of solid *M. leprae* in smears or biopsies; and (2) infectivity to mice of *M. leprae* taken from leprosy patients by tissue biopsies. Using these laboratory criteria, infectiousness is *not* determined by the patient's Bacteriologic Index (total numbers of AFB in smears or biopsies), but instead by his MI, and particularly by the results of mouse inoculation. Even if still heavily bacteriologically positive, a patient is assumed no longer infectious if his MI is 0%, and particularly if *M. leprae* obtained from his biopsy fails to multiply in mouse footpads.

The original study by Shepard, Levy and Fasal (83), and a series of "short term" drug trials (i.e., based on serial mouse footpad inoculations of *M. leprae* obtained from the patients during the first six months of therapy) currently being conducted in Cebu have definitely shown that *M. leprae* taken from lepromatous patients after 90 days of standard DDS therapy are no longer infective to mice. It has been deduced from this finding that lepromatous patients are made virtually noninfectious (i.e., infectiousness is reduced by more than 99% from pre-therapy levels) by only 90 days of therapy with DDS. This assumption is important, because it may be taken to mean that current leprosy control measures can be reduced to a minimum, i.e., to treatment of all patients and contacts for 90 days. Epidemiological evidence to the effect that the infectiousness of lepromatous patients is markedly—but not completely— reduced by DDS therapy long before they become bacteriologically negative, is shown or at least suggested by the rather limited and mainly retrospective studies by Worth in Hongkong (93, 94) and by Razi et al in Venezuela (72), and also that by Figueredo et al (31) in Bombay.

In view of the implication to epidemiology and control, however, Bechelli and Guinto (4) and others have urged that the above assumption should first be confirmed by more definitive clinical and epidemiological studies before being accepted. Evidence is cited against the finding that lepromatous patients are rendered noninfectious after a few months of DDS therapy. As shown by now increasingly available literature (4, 71), relapses occur in many lepromatous patients rendered bacteriologically negative by 5 or more years of continuous treatment with 50 to 100 mgm. of DDS daily, and presumably even in patients who continue taking DDS after becoming bacteriologically negative. Attention was also called to the results of the Chingleput chemoprophylaxis trial (14, 25, 26) in *healthy* children living with lepromatous index cases. Over 5½ years of actual observation in this strictly controlled double-blind study, leprosy developed in 48/360 or 13.3% of untreated healthy child contacts receiving placebos; but significantly, also in 23/359 or 6.4% of the children treated prophylactically with DDS at doses approaching standard therapeutic doses. The authors also pointed out that 25 years of DDS therapy all over the world, in leprosy patients who must all be considered overtreated if judged by mouse infection standards, has not significantly lowered the prevalence of leprosy on a world-wide basis.

Manner of Transmission

Portal of entry. The exact mode of transmission remains unascertained. As said, tremendous numbers of *M. leprae* are discharged from the skin lesions and nasal mucus of "open" cases (16, 69). However, judging from the very low MI or percentage of solid bacilli in untreated cases in Cebu and elsewhere (i.e., 4% to less than 1%), only a very small proportion of the discharged bacilli may be infective.

For a long time the prevailing opinion has been that the bacilli usually enter the body through wounds in the skin, by direct person to person or skin to skin contact, or through fomites. If the point of entry is the skin, a break in continuity through injury, dermatoses or insect bites must be necessary, because *M. leprae,* uncultivable under the best conditions, is certainly unable to penetrate

intact skin. In support of the cutaneous route, Rogers and Muir (80) long ago observed that initial lesions were more frequent on the feet and legs of patients from stony regions of India than in those from places where the soil was alluvial. Two often quoted instances of accidental cutaneous transmission are the Marchoux report (57) of a medical attendant whose finger was pricked during an operation for the removal of a lepromatous nodule, and who developed an anesthetic, bacterio-positive lesion around the site of the puncture some years later; and that by Porritt and Olsen (70) of two Marines from Michigan who were tattooed at the same time in Australia during World War II, and who both developed classical tuberculoid leprosy in the tattooed areas 2½ years later.

Nolasco and Lara (68) made a noteworthy study in Culion of a 15-month old child with a solitary lesion on the right knee and who died suddenly of pneumonia. Detailed histopathological study at autopsy revealed the lesion on the knee to be a leproma, but after an exhaustive search no other findings were seen in the child's body except a few AFB in one right inguinal lymph node. The authors concluded that the lesion on the knee of this child, as well as those of numerous instances of solitary lesions they had seen in children of Culion pattents (51), were primary foci (i.e., the point of entry) and not the result of hematogenous dissemination.

Many new or early cases of leprosy in Cebu show no finding except minimal single lesions of nonlepromatous appearance and histopathology. For example, 23/76 or 30.2% of all the new cases of leprosy discovered during a re-examination of the population of Cordova in 1967 consisted of cases with small solitary lesions. It is logical to assume that these single lesions constitute the actual sites of inoculation through the skin, as concluded by Lara and Nolasco (51, 68) and many others.

In a new report by Bechelli et al (5) the particular sites of the solitary lesions of tuberculoid and indeterminate leprosy in 469 Burmese child patients were as follows: buttocks and thighs 37.7%, upper extremities 33.1%; legs and feet 13.8%; trunk 12.7%; and face 2.5%. It was deduced that in Burma the predilection of single early lesions for certain regions of the body did not appear to depend on whether these parts were exposed or not. In a much earlier Cebu study (19), the locations of the first lesions in 79 patients with reliable examinations were as follows: buttocks and thighs 42.1%; upper extremities 26.3%; legs and feet 23.7%; trunk 3.9%; and face 4%. It has been argued, with reason, that if the portal of entry in leprosy were purely cutaneous, the feet and legs, upper extremities, and/finally the face should show the highest frequencies of primary foci instead of the buttocks and thighs, because the latter are relatively unexposed.

Aside from the fact that nasal secretions from lepromatous patients have been shown to contain numerous infective *M. leprae* (16, 69), there is increasing opinion to the effect that the skin is not the usual and much less the only portal of entry in leprosy. Weddell et al (91) found solid AFB in the Schwann cells of biopsied nerve twigs taken at points far removed from the single lesions of some nonlepromatous patients. They have concluded that *M. leprae* must disseminate *primarily* via the blood stream. In line with this finding, Weddel et al (91), Newell (67) and lately Rees and Meade (75) are of the opinion that the passage of *M. leprae* through the upper respiratory tract is a much more likely route of infection than cutaneously. It is pointed out that initial or solitary skin lesions are possible with systemic spread (assuming a nasopharyngeal route), because such lesions could conceivably be caused by trauma as a localizing factor.

Newell has long contended, with reason, that most of the epedemiological features of leprosy are better explainable by a respiratory than a cutaneous route of infection. Rees and Meade state that the numbers of *M. tuberculosis* in sputum from open cases of tuberculosis, and of *M. leprae* in the nasal secretions of lepromatous patients are similar; and that attack rates in families and contacts are likewise similar for both diseases, so that by analogy, tuberculosis and leprosy are likely to have the same manner of transmission.

From the foregoing, it would appear that leprosy may be spread either percutaneously or by inhalation. Solitary nonlepromatous lesions appear more likely to be primary foci rather than secondary sites localized by trauma. It is probable that most lepromatous cases are infected via the respiratory route. In Cebu, very few lepromatous cases have been observed to develop from early single lesions.

Skinsnes (75) has recently reminded IJL readers that the view of the spread of leprosy

through the nasal mucosa is by no means new. He quotes Leloir (1886), Goldshmidt (1891), Mouritz (1916) and Jeanselme (1934) as having already suggested long ago that infection might take place by inoculation at broken skin surfaces or inhalation through mucous surfaces; and also that Rogers and Muir had commented in 1946 on "the commonly held view that the organism may find access through abrasions of the skin or the nasal mucous membrane".

The case for transmission by arthropods. Since it is virtually certain that *M. leprae* is unable to penetrate intact skin, a number of authors, particularly Dungal (28, 29) and Munos Rivas (61, 62) have long been convinced that biting or blood-sucking insects are logical and even obligatory transmitters of leprosy (i.e., analogous to typhus and plague). The fact that attack rates are 4 or more times higher among household contacts of lepromatous cases than others could be attributable to transmission by housebound or nonflying insects such as fleas, bedbugs, lice or the acarinae of scabies, all of which are extremely common in all areas where leprosy is highly endemic. Despite working in close contact with leprosy patients, the disease is *not* unduly frequent among the medical and nursing staffs of leprosy institutions. Leprosy also does not seem to spread when introduced into cities or areas where the disease is currently nonendemic. It has been put forth that these epidemiological observations are explainable by the presence or absence of insect vectors of household range.

Large numbers of AFB have long been found in the stomachs of insects. As cited by Dungal (28, 29), Sandes as early as 1912 found AFB in 20/60 fleas and in 20/75 bedbugs fed on leprosy patients. Munos Rivas (28, 29, 61, 62) found AFB in 32/200 or 16% of the fleas caught in a leprosy clinic in Colombia, but presumably in none of 575 fleas caught in places free from leprosy. He also examined 1627 fleas fed experimentally on leprosy patients and found AFB in 187 or 11.4% of them. Munos Rivas likewise reported finding many AFB in the intestine of Acarus scabiei collected from dwellings of leprosy patients.

The flea (Pulex irritans) has been considered a prime suspect in Colombia and in Iceland by Munos Rivas and Dungal, respectively. The flea is said to live as long as 500 days, may stay hungry for weeks waiting for a chance to suck blood, and its bite easily reaches the dermis. The bedbug (Cimex lectularius) is a very common household and bedroom insect in the Philippines. Like the flea, bedbugs have a long life, can live a long time without drawing blood, and attack people in bed, piercing right into the dermis. If *M. leprae* could remain viable for long periods in their digestive tracts, fleas and bedbugs might account for some untraceable infections.

Scabies has been associated with leprosy since the time of Danielssen and Boeck. The frequency of scabies has been taken as a rough indicator of leprosy by Innes (46) and others. Aside from the burrowing of female mites into the epidermis, infected and ulcerated scabies would facilitate the entry of *M. leprae* through the skin. AFB have also long been found in mosquitoes (28, 29). However, leprosy might be expected to be more widespread and less limited to households with primary cases if flying insects with a relatively wide range of movement were significant transmitters of the disease. Lice do not appear to be likely vectors; they are short-lived, have no mobility and die in a few days if unable to suck blood.

Transmission by arthropods, however likely, has been impossible to prove so long as *M. leprae* remains uncultivated and untransmitted to experimental animals. The identification of *M. leprae* by Shepard's mouse footpad technique has now provided investigators with a possible means of verifying insect transmission, and it is gratifying that valuable experimental work in this field has been conducted by the USPHS-JIPMER (Jawaharlal Institute of Postgraduate Medical Education and Research) project in Pondicherry, India, headed by Dr. Kirchheimer.

In a series of recent articles (55, 56, 65, 66), The USPHS-JIPMER group of investigators have reported the following: (1) Bacillemia was found in 100% of 38 untreated lepromatous patients, and in none of 15 tuberculoid patients; and mouse footpad inoculation for *M. leprae* was positive in 7/15 patients with bacterimia. (2) Laboratory-reared Culex fatigans and Cimex hemipterus were fed on untreated lepromatous patients; 27/38 or71% of the mosquitoes and 18/35 or 51% of the bedbugs ingested AFB as seen by microscopy; and two mouse inoculation trials with mosquito homogenates were positive for *M. leprae*. (3) Mosquitoes, bedbugs, head lice

and scabies mites were collected from dwellings of lepromatous patients, and from control dwellings without leprosy. Arthropod pools obtained from patients' dwellings were microscopically positive for AFB in 4.1% of Anopheles, 3.6% of Culex, 7.4% of Pediculus and in a single pool of Sarcoptes. However, in the control dwellings, AFB were also found in 7.7% of Anopheles, 6.8% of Culex, 9.2% of Cimex, in none of Pediculus, and in 2/3 Sarcoptes pools. Positive mouse footpad inoculation was found in 2 Culex pools, 1 collected from patients' dwellings and other from controls. (4) Laboratory-reared mosquitoes and bedbugs fed on lepromatous patients were inoculated into mouse footpads at various time intervals after feeding. *M. leprae* was reported viable for a minimum of 5 days in the digestive tracts of Culex fatigans and for 4 days in Cimex hemipterus. The authors have concluded with reason that arthropods are very capable of ingesting and retaining viable *M. leprae* for certain periods and must be considered very capable of transmitting leprosy.

It is possible that final proof of transmission of leprosy by arthropods may be obtained by exposing armadillos to appropriate arthropods which have been fed on untreated lepromatous patients, or obtained from the dwellings of newly discovered (i.e., untreated) lepromatous cases.

Broad Epidemiological Features

Race. Leprosy occurs in all races, whether black, brown, yellow or white. No reliable comparisons of relative resistence by race are possible, because of the lack of incidence figures for different racial groups living under equal conditions of exposure as well as environment. Hayashi (45) in 1935 probably first noted the great variation in the severity of leprosy in different parts of the world. The relative frequency of two polar types varies greatly, racially and geographically. In general, only about 15% of all known cases in India are lepromatous, compared to 40% to 50% or more among Caucasians, Japanese, Chinese and Koreans. The lepromatous rate may vary from 30% to 40% in Burma, Thailand, Malaysia and the Philippines. In the hyperendemic areas of Africa, however, lepromatous cases may constitute less than 10% of the total prevalence.

Distinct variations, geographic as much as racial, have also been noted concerning certain clinical manifestations. The maculo-anesthetic and primary polyneuritic types of tuberculoid leprosy are much more common in India than elsewhere. The diffuse necrotizing form of lepromatous leprosy described as "Lucio" leprosy is apparently found exclusively in Central America, particularly in Mexico and Costa Rica. Lepromatous alopecia is said to be observed only in Japan. The reasons for such racial and geographic variations are not clear. Genetic variability is implied, both human and in the leprosy bacillus. Although different strains of *M. leprae* from various parts of the world have shown similar growth patterns in mouse footpads, this does not mean that they may not have different pathogenicities.

Sex. Prevalence and incidence figures are consistent everywhere in the absence of any sex difference in the tuberculoid type of leprosy at any age. Equally consistent are prevalence rates all showing a significantly greater frequency of the lepromatous type in the male sex, though usually only in persons over 14 years of age. The sex variation in lepromatous leprosy has ranged from 1.5 to 3.0 males to each female.

The excess of the lepromatous type in males has been shown in a Cebu study (2) to be caused by a higher attack rate and not because of longer duration of the disease in the male sex. The average attack rate for lepromatous leprosy was 1.8/1000/year in males compared to 0.8/1000/year in females, while the average duration was estimated at 15.7 years in males and 15.4 years in females. Some excess of lepromatous leprosy was also seen in the attack rate among male children, further indicating that males are inherently more susceptible. It would be necessary, however, to show a significantly higher lepromatous attack rate in males during childhood, where contact opportunities are approximately equal for both sexes, for definite proof of a sex difference in susceptibility. No such figures are yet available, in part because of the very low incidence of the lepromatous type in early childhood and in children under 10 years of age.

Age. Leprosy occurs from infancy to old age. Isolated instances of leprosy in infants were reported by Dreisbach (27) at 7 months, by Rodriguez (79) at 8 months and by Lara (46, 68) at 9 to 11 months of age. As cited by Newell (67), Lara observed that 66% of 200 children born in Culion and not isolated at birth developed some form of leprosy before the age of 2 years; 36% of these children

showed lesions between the ages of 3 and 6 years; and significantly, the lesions, mostly of minimal nature, healed spontaneously in 77% of the cases before the children reached adolescence. During the years before sulfone therapy, Rodriguez and others including the writer have observed many instances of small, solitary and anesthetic lesions in children which disappeared without treatment within 1 to a few years. These self-healing minimal infections are certain to be missed unless seen during their active stage.

Leprosy also manifests itself for the first time in the aged. In a resurvey of a community in Cebu (34), 13 cases—10 tuberculoid and 3 lepromatous—were discovered in persons over 50 years of age, 11 of whom had been previously examined and found without leprosy. In a single year, 43 new cases—33 tuberculoid and 10 lepromatous or borderline—were discovered among the consultations at the Cebu Skin Clinic in persons over 50 years of age, of whom 10 were more than 70 years old; and the average stated duration of the lesions in these cases was 2.06 years.

It is a fact that children are much more susceptible than adults. In the Cebu studies (20, 34), the peak of the attack rate was found in the age group 10-14 years, both for lepromatous and tuberculoid leprosy, and among household contacts as well as in the rest of the population, although the median age was younger among household contacts. A rapid decline took place after adolescence, but new cases still occurred in adults.

Doull (23) has noted that in highly endemic areas, the average age when the first signs are detected is very much earlier than in areas where the disease is rare. In Texas, for example, Kluth (49) found that the average age at stated onset was 40 years, as compared with the maximum attack rate in Cebu at 10-14 years. Doull concluded that the age at which leprosy is contracted depends primarily on opportunities for exposure, and that the explanation for the rapid decline in attack rates after adolescence in highly endemic areas was the acquirement of resistance, due to still unascertained causes.

The Question of Genetic Susceptibility to Leprosy

An inherited predisposition to leprosy has long been suspected, which implies that some persons may have one or more genes which make them more susceptible than those with the alternate genotype; but appropriate exposure to *M. leprae* infection is of course still necessary to cause disease. Evidence for genetic factors in leprosy is considered in this section.

Racial and geographic variations. Apart from the marked racial and geographic variability in clinical manifestations mentioned in the section on Broad Epidemiological Features, it is reported that expatriate racial groups tend to continue developing the particular types of leprosy to which they were susceptible in their own native lands. It is said that in Brazil and South Africa, the disease is more severe in whites than among the natives; in Malaysia, the lepromatous rate is higher among Chinese compared to Indian settlers; in Burma, the Burmese suffer from a more serious disease than Indians; and in India, there is more lepromatous leprosy among Anglo-Indians than in pure blooded Indians. This naturally suggests the existence of human genetic factors which may vary according to race, since environmental influences are somewhat minimized.

Familial aggregation of cases. Leprosy is not randomly distributed in communities and occurs more frequently in certain families than in others, suggesting a possible familial segregation of genes with differing susceptibilities. This concentration in families, however, may be due as much to increased exposure as to hereditary predisposition. Children of leprous parents isolated at birth do not develop leprosy as often as unisolated children, and many reports tend to show that the risk of leprosy in child contacts increases both with duration and intimacy of the contact. Unfortunately, no studies are possible of sex and age-specific attack rates in persons directly related to a primary case in the family as compared to those not related but equally exposed to the same primary cases.

As reported by Aycock and McKinley (1), leprosy clusters developed among French Acadians expelled from Nova Scotia in 1877 and who migrated either to nearby New Brunswick or to Louisiana. Assuming complete ascertainment of data, which is unlikely, Spickett (85, 86) analyzed two pedigress of a large kinship from the new Brunswick group, using a sibship method. He concluded from this limited analysis that leprosy may be inherited as a simple autosomal irregularly dominant trait, with up to 83% "penetrance" of the gene. A number of pedigree and sibship studies of leprosy have been reported,

but all are questionable because of conflicting results and obvious shortcomings in the material. It may be concluded that no specific mode of inheritance, if it exists, can yet be determined from available family data on leprosy to date. Recent advance in the techniques of segregation analysis promise better chances, but still contingent on the collection of accurate family data.

Leprosy in twins. Twin studies are considered an important tool for indicating genetic susceptibility, because the strong environmental component which characterized leprosy would be minimized in such studies. Mohamed Ali and Ramanujam (60) have reported a notable study conducted in South India, of leprosy in 35 pairs of twins—23 monozygotic (identical) and 12 dizygotic (fraternal). Aside from identical appearance and sex, monozygosity was presumably affirmed by blood group and fingerprint determinations. The results are summarized in Table 2, to which the writer has added a small number of observations of leprosy in twins in Cebu (40). The Cebu figures consist of 4 pairs of monozygotic twins, all young females of identical-twin appearance and 1 pair of young dizygotic twins of opposite sex.

Taking the combined figures of Table 2(a), among 27 monozygotic pairs, concurrent leprosy of the same clinical type occurred in 20 (70.1 %), and of dissimilar type in 3 (11.1 %), while in 4 (17.4%) leprosy was found in only one member of each pair. In marked contrast, among 13 dizygotic pairs, 1 (7.7%) showed concurrent leprosy of similar type, 1 (7.7%) also of dissimilar type, while no less than 11 (84.6%) showed leprosy in only one member of the pair. The very high concordance for leprosy among the monozygotic twins, along with the equally high discordance among the dizygotic twins, strongly suggest a hereditary factor in leprosy. No less than 20 or 87% of the 23 affected monzygotic pairs developed the same type of disease presumably at about the same time.

The writer has not read the new monograph (15) by Chakravartti and Vogel (i.e., a Twin Study on Leprosy), except for a table showing the figures in Table 2(b), in which no distinction was made for leprosy in only one of each pair among the 102 pairs of twins—62 monozygotic and 40 dizygotic—included in their study. It would appear that dissimilar and single infections among twins were both consi-

TABLE 2

CONCORDANCE OF LEPROSY IN MONOZYGOTIC AND DIZYGOTIC TWINS

Study	Zygosity	Twin pairs examined	Leprosy in both members: Similar type (concordant)	Leprosy in both members: Dissimilar type (Discordant)	Leprosy in one member only (Discordant)
(a) Mohamed Ali & Ramanujam, and Guinto:					
India (1)	Monozygotic	23	17 (73.9%)	2 (8.7%)	4 (17.4%)
	Dizygotic	12	1 (8.3%)	1 (8.3%)	10 (83.3%)
Philippines	Monozygotic	4	3 (75.0%)	1 (25.0%)	0
	Dizygotic	1	0	0	1(100.0%)
	Monozygotic	27	20 (74.1%)	3 (11.1%)	4 (14.8%)
	Dizygotic	13	1 (7.7%)	1 (7.7%)	11 (84.6%)
	TOTAL	40	21 (52.5%)	4 (10.0%)	15 (37.5%)
(b) Chakravartti & Vogel:			(Concordant)		(Discordant)
India (2)	Monozygotic	62	37 (59.7%)		25 (40.3%)
	Dizygotic	40	8 (20.0%)		32 (80.0%)
	TOTAL	102	45 (44.1%)		57 (55.9%)

dered discordant by Chakravartti and Vogel. Their findings, as seen in Table 2(b), also show a higher concordance for leprosy in identical as against fraternal twins, although much less than in the Mohamed Ali and Ramanujam report.

Even genetic studies in twins should be interpreted with some caution. Aside from the usually limited numbers and doubts as to the reliability of zygosity determinations, there is often a high degree of selection in such studies, because the disease (particularly leprosy) in both members of a pair is more likely to call attention than disease in only one member. Monozygotic twins, aside from having the same sex, also share more identical conditions of environment than dizygotic twins, so that even traits not considered hereditary such as homosexuality and criminal behavior are said to be more common among the former. Nonetheless, and although the figures in Table 2 do not sugest the mode of inheritance, the foregoing twin studies provide important suggestive evidence in favour of genetically determined predisposition to infection with *M. leprae*.

Leprosy and genetic polymorphisms. Aside from major and minor blood groups, many genetic systems have been investigated for possible association with leprosy. A significantly higher or lower frequency of a known genetic marker in leprosy of either polar type, as compared to controls, would imply the possible involvement of some human genetic factor, although it would still be necessary to determine the mechanism by which the genetic marker in question may affect individual resistance or susceptibility to leprosy. LeChat (52) has reviewed the extensive literature available concerning the ABO blood groups in leprosy and condensed them into a single table; the findings in this table are contradictory even among the more reliable reports, and it is certain from this review that there is no striking association between leprosy of any type and the ABO blood groups. In a well-controlled study (52). LeChat et al also failed to find any very significant association between lepromatous or tuberculoid leprosy and the ABO, Rh, MNSs, Kidd, Kell, Cellano, Duffy, Lutheran and Pl blood group systems.

Beiguelman (7) appears to have found a lower frequency of taste sensitivity to phenylthiourea (PTC) in leprosy patients as against controls, but did not relate this finding to any particular type of leprosy. LeChat et al (53) likewise tested large groups of lepromatous cases, tuberculoid cases and controls for comparative frequencies of the sex-linked enzyme, glucose-6-phosphate dehydrogenase (G6PD), and of 4 genetically controlled serum proteins—haptoglobulins, transferrins, group-specific component (Gc) and the beta-lipoprotein Ag. These authors found some association between haptoglobulin polymorphism and leprosy, but caution was recommended in the interpretation of this particular finding until confirmed by others. So many comparisons between leprosy cases and controls have been made concerning genetic polymorphisms that some statistically significant differences may turn up purely by the operation of chance.

Leprosy and Australia Antigen. Australia Antigen or Au(1) (also known as hepatitis associated or HA Antigen) is closely related to the hepatitis virus, if not part of the virus itself. Au (1) is found only transiently or within days to a few weeks in patients with acute virus hepatitis. Individuals with persistent Au (1) in the blood for months or years, however, are usually without symptoms and could be carriers of the hepatitis virus.

From extensive tests (involving several hundreds of lepromatous cases, tuberculoid cases and controls) by Blumberg et al in Cebu (9, 10, 11, 12), South India (13) and elsewhere, it was established that there was significantly higher frequency of Australia Antigen in patients with lepromatous leprosy (Phil; 10.1%; India 6.2%), than in patients with tuberculoid leprosy (Phil. 4.3%; India 2.1%), or in persons without leprosy (Phil. 5.0%; India 2.0%) from the same area. Au (1) was more common in males than in females, and its frequency decreased with increasing age, thus simulating the distribution of lepromatous leprosy. Institutionalized lepromatous patients did not have a higher frequency of Australia Antigen (8.8%) as compared to lepromatous patients living at home (11.9%), minimizing institutionalization as a selective environmental factor. Lepromatous patients in Cebu retested for Au (1) after 1, 2 or 3 years showed considerable persistence of the trait after 1 or 2 years, but this persistence decreased after the third year (12). Lepromatous patients positive for Au (1) were reported with slightly elevated SGPT levels, suggesting that they may have chronic anicteric hepatitis (11).

The cell-mediated immune response is involved in resistance to infection with

mycobacteria as well as viruses, both being intracellular parasites. It is now known that cellular immunity is depressed in lepromatous leprosy, and that the impairment of CMI is both specific and of generalized nature. For the latter reason, lepromatous patients would be expected to be more susceptible to chronic virus hepatitis than tuberculoid patients or controls, and thus to show detectable Au (1) for extended periods.

In addition, however, Blumberg et al (12) conducted family studies of Australia Antigen in Cebu and in Bougainville, New Guinea. They have reported that a segregation analysis of both studies showed a familial distribution of Au (1) which was consistent with that of simple autosomal recessive Mendellian inheritance. As a result, they offer an alternate interpretation for the association between Australia Antigen and lepromatous leprosy. Individuals homozygous for a postulated gene designated Au^1/Au or Au/Au. The postulated gene which in double dose (Au^1/Au^1) confers increased susceptibility to chronic hepatitis may also confer susceptibility to infection with some other immunologically related organism, such as *M. leprae*. Thus, in areas where both gene and the related organisms are common, as in the Philippines and India, there would be a correlation between chronic hepatitis and lepromatous leprosy. The assumption is further made that, as may sometimes occur, bearers of Au /Au genes may be at some advantage when infected with the hepatitis virus in that they develop mild and even subclinical symptoms; but these same homozygous bearers of susceptibility genes may suffer a compensatory disadvantage in that when chronically infected with the other related organism, *M. leprae* in this instance, they may develop serious disease or lepromatous leprosy. The authors carefully emphasized the very conjectural nature of this genetic hypothesis and recommended further investigations to confirm its existence.*

Genetics and reactivity to lepromin. The early (Fernandez) reaction to lepromin is a delayed-type hypersensitivity reaction, and the late (Mitsuda) reaction is a tuberculoid granuloma, occasionally referred to as a delayed-type hypersensitivity granuloma. Both are expressions of competent cellular immunity. In analogy with tuberculoid lesions, it is considered that a positive Mitsuda reaction additionally prespupposes the ability of tissue macrophages to phagocytize and to lyse the killed *M. leprae* in the lepromin before being able to change, or rather to mature, into the epithelioid and giant cells characterizing the nodular late lepromin reaction. For this reason, the granulomatous Mitsuda reaction is probably more indicative of resistance than the allergic Fernandez reaction. In certain immunological conditions, hypersensitivity is not positively associated with resistance.

Mainly on the assumption that the total prevalence of lepromatous leprosy is always lower than the total prevalence of lepromin-negative persons in any population, it has been suggested by Newell (67), Turk (90) and some others that the development of the disease is associated with a host-determined characteristic present only in a small but fixed proportion of individuals. Rotberg, for example, believes that certain individuals are born without a designated "N-factor", and as a result are incapable of ever becoming lepromin-positive at any age and under any provocation, whether by BCG vaccination, repeated lepromin testing, leucocyte transfers or "Transfer Factor". Only persons lacking the so-called N-factor are presumed to develop lepromatous leprosy upon infection. It has also been reported (6) that cultures of blood macrophages from lepromatous patients anergic to lepromin are unable to lyse *M. leprae* but can lyse other mycobacteria, whereas macrophages from Mitsuda positive tuberculoid cases and controls can lyse *M. leprae* as well as other mycobacteria. None of the foregoing observations can be considered confirmed, but all suggest a genetic basis for lepromin reactions and that only primarily lepromin-negative individuals may develop lepromatous disease.

Very large numbers of normal persons of all ages have been lepromin-tested in Cebu in the course of a series of published lepromin studies (21, 35, 36, 37, 38, 39, 41). The population is extremely reactive to lepromin, even at the conservative 5 mm. level of positivity adopted in Cebu. Infants are lepromin-negative but adults are almost universally lepromin-positive. Reactivity to lepromin increases very sharply with each year of age during childhood, this from natural causes and without the benefit of BCG vaccination. Significanly, no differences were observed in the frequency of Mitsuda reactions according to sex or age, between families of lepromatous cases, families of tuberculoid cases, and families without known leprosy (36). The Cebu lepromin findings do not support a

* Only a prospective study can establish the validity of this hypothesis—Editor

genetic hypothesis for reactivity to lepromin and disagree with a more limited study by Beiguelman (6,8) which apparently showed that children born of lepromin-negative parents (lepromatous cases) were definitely less reactive to lepromin than the children of lepromin-positive parents.

Healthy adults in Cebu generally remain lepromin-positive most of their lives. Purely lepromatous cases tend to remain lepromin-negative many years after becoming clinically inactive and bacteriologically negative following treatment with sulfones. In 1974, however, more than 100 formerly lepromatous and borderline cases who had been discharged 5 to 10 or more years from the Eversley Childs leprosarium in Cebu were lepromin-tested; and 51 or 50% were or had become Mitsuda positive. Lepromatous cases are usually tested and found anergic to lepromin after the disease has developed; and previous reactivity, whether positive or negative, is not known. It is possible for such cases to have been originally lepromin-positive and to have lost it upon developing the disease. At least 4 instances have been noted in Cebu (40) of lepromatous leprosy in lepromin-positive persons (tested before they developed the disease) who became lepromin-negative when the disease appeared, although none of the 4 had a strongly postitive Mitsuda reaction at the outset.

Following exacerbations or clinical worsening, tuberculoid cases may change to "tuberculoid in reaction", and indeterminate cases more often than tuberculoid ones into instances of "reactional tuberculoid" leprosy. Under the newer Ridley-Jopling classification (77,78), these are considered transformations into the various borderline types of leprosy, ranging from BT to BL. It is now established that initially positive Mistuda reactions often become weakened or completely negative during these clinical transformations (2, 3, 40, 42); but they occur only when hematogenous dissemination (bacteremia) develops, as shown by bacteriologic positivity and widespread lesions in the patients. Furthermore, the lost reactivity often reverts to its former positive state when the lesions subside. Several instances have also been noted in Cebu (42) of lepromin-negative cases of still indeterminate leprosy in adults who, on subsequently turning tuberculoid, became Mitsuda positive. These well substantiated changes in reactivity to lepromin do not suggest a genetic component. Instead, the anergy in lepromatous leprosy could be partly and even largely of secondary nature, indicating a depression of cellular immunity resulting from the disease itself. The mechanism of this secondary depression of cellular immunity in lepromatous leprosy has so far remained uncharacterized.

Comment. A genetic susceptibility to leprosy is suggested by the observations reviewed in this section. In sum, however, there is yet no firm evidence of such a genetic factor, and further studies are needed. Priority might be given to the problem of a genetic basis for reactivity to lepromin, and as to whether the familial aggregation of lepromatous vs. tuberculoid leprosy follows any definite pattern of Mendelian inheritance, such that the spread of the disease may be predicted from it.

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TRANSMISSION OF LEPROSY

J. C. PEDLEY

AN ERRONEOUS CONCEPT

An erroneous popular concept of the transmission of leprosy which has been accepted by generations of leprosy workers is the hypothesis that the disease is spread by skin to skin contact; and that so long as bacilli can be found in the skin, even though few in number and in non-morphological form, the patient is still infectious. This erroneous concept has been responsible for perpetuating the stigma of leprosy and prolonging the mental suffering of the one so afflicted, because he is denied access to society and employment.

During recent years 4 discoveries have radically altered this age-old concept of the transmission of leprosy.

These are:

(1) The enumeration of M. leprae on the surface of intact skin.

(2) The enumeration of M. leprae discharged in the noseblow of a lepromatous patient.

(3) The viability of the M. leprae (discharged in the noseblow) outside the human body.

(4) The rediscovery of the long neglected work of Schäffer (1898) on the release of M. leprae from the upper respiratory passages.

1. The enumeration of M. leprae on the surface of intact skin

For many years it was believed that leprosy bacilli escaped from the surface of the skin in "great", "large", "enormous", "innumerable" numbers (to quote some of the adjectives used in the literature). This belief, which was purely hypothetical, led to another namely that the transmission of leprosy took place over a prolonged period by skin to skin contact. Although this postulate was never proved, it was regarded as the main method of transmission by generations of leprosy workers. It was not until 1969 that this hypothesis was scientifically challenged. The author, using a method which he called the COMPOSITE SKIN CONTACT SMEAR (CSCS) method (1), in which every field searched was actually 10 fields, examined one million consecutive microscope fields of very infiltrated and highly bacilliferous intact skin of 28 untreated lepromatous cases (2). This search took about 70 hours of microscope work—spread over a period of 14 months. Only 52 acid fast bacilli were found, whose presence was associated with noseblows heavily infected with M. leprae, and they were found on skin READILY ACCESSIBLE TO THE FINGERS, suggesting that in all likelihood they were transferred to the skin from the nose. It may be said that by the CSCS method, a scientific attempt was made to collect bacilli from the orifices of countless sweat-gland ducts and hair-follicle openings. That so few bacilli (whose probable origin was the nose) were found in this prolonged search, appears to be clear evidence that M. leprae are rarely, if ever, discharged on the surface of intact skin by the skin's secretory apparatus.

2. The enumeration of M. leprae discharged in the noseblows.

In addition to examining the noseblow smears of these 28 lepromatous patients (most of whom showed smears loaded with bacilli and numerous globi), the author continued for a period of several years to examine the nasal mucus discharge for the presence of leprosy bacilli in more than 700 patients suffering with all types of leprosy both in the untreated and treated stages. It needs to be emphasised that in this type of smear NO ABRASION IS MADE IN THE NASAL MUCOSA. The smear is made, either from mucus blown out of the nose, or mucus gently collected from the surface of the mucosa with a platinum loop. In a previous paper (3), the findings in 322 of the above 700 patients is described. It was read in substance at the 10th International Con-

gress in Bergen in 1973, and was copiously illustrated with colour photomicrographs showing bacilli escaping from the UN-BROKEN nasal mucosa. Briefly the findings can be stated as follows:

First: In the great majority of untreated LEPROMATOUS cases, the nasal mucus discharge smears are positive for leprosy bacilli: often there are enormous numbers of bacilli in these smears.

Second: The morphological index of the bacilli in the nasal mucus smears is usually much higher than in the skin-slit scrape smears.

Third: Generally speaking, after 4 to 5 months standard treatment, morphologically normal bacilli are no longer found in nose-blow smears: indeed, it may be difficult to find any acid-fast organisms.

Fourth: The nasal mucus discharge smears in BORDERLINE leprosy are rarely positive for bacilli, even though there are numerous reactive lesions on the face and body.

Quantitative estimates of M. leprae present in the noseblows from untreated lepromatous patients, have been carried out by Dr. Rees, and have revealed enormous numbers of M. leprae.

For example, in a specimen measuring approximately 1 ml. of mucus blown out in one noseblow, (sent to Dr. Rees by the author) he found it contained in the region of 20 million bacilli. In a 24-hour collection of noseblows from a patient with advanced lepromatous leprosy, Dr. Rees found 380 million bacilli, 30 million of which were morphologically normal. The author has often found patients with NON-APPARENT lepromatous leprosy (Fig. 1) discharging many bacilli in their noseblows (1).

3. The viability of M. leprae outside the human body.

How long can the M. leprae from the nose-blow remain viable outside the human body? Dr. Davey (4), working in Dichpalli in central India, sent specimens of highly infected nose-blows (packed on ice) from over thirty un-treated lepromatous patients to Dr. Rees in London. By special arrangement with the airways, it was possible for these specimens to reach Dr. Rees' laboratory in 24-30 hours. In every case, Dr. Rees obtained multiplica-tion of bacilli in the footpads of mice (with artificially depressed cell immunity). By this method also, Dr. Rees showed that the leprosy bacillus could remain viable, at laboratory temperatures, for up to 42 hours, after remo-ving it from the ice on which it was packed. This finding was reported at the Bergen Con-ference (1973), and later, that same year, Dr. Rees established by viability tests, that the bacillus could remain viable outside the body even up to seven days.

4. The rediscovery of Schäffer's findings on the release of M. leprae from the upper respiratory passages (5)

In 1898 at the first International Leprosy Congress at Berlin, Schäffer described experi-ments in which sets of microscope slides were placed at distances up to 50 cm in front of 2 patients with severe lepromatous leprosy during the process of talking, coughing, and sneezing. Large numbers of acid-fast bacilli were found on the slides. At that time it was impossible to identify these as Myco-bacterium leprae, and Schäffer's work suffered from the neglect which for so many years surrounded nasal infection in leprosy, on the grounds that authentic M. leprae could be confused with contaminating acid fast bacilli at this site. His original paper was written in German. In 1973, Dr. Rees arranged for its translation into English by Dr. Bodin-gius (copies of which are available on applica-tion to the Leprosy Study Centre in London), and the relevant sections are as follows:

"20-30 glass slides, closely adjacent, were placed in front of the patient. The patient talked for 10 min, reading or counting, after which time the slides had on them specks of mucus of different sizes. The slides were left till dry, fixed over flame, and stained by the Ziehl-Neelsen method. For counting slides were divided into 8 quadrants, numbers of acid-fast bacilli in each quadrant were counted using oil immersion lens, and the total number of bacilli then calculated. Mistakes were avoided by decolourising with acid alcohol, bacilli about which there could be no doubt showing characteristic cigar shaped bundles and the occurrence of conglomerates (globi). No bacillary complexes were counted, only single organisms. It was found that if the patient stood upright, drop-lets were projected as far as 30-50 cm onto surfaces held in front of the patient.

Results. One patient released 10,000 to 25,000 bacilli. The other patient released 75,000 to 120,000 bacilli and on one occasion 185,000 bacilli. In both patients investigated the secretion from the nose contained very

many bacilli. Extremely large numbers of bacilli were released in sneezing (patients were given sneezing powder) ... in one sneeze a patient released 110,000 bacilli.

Conclusions. Leprosy patients with mucous membrane affection of the respiratory tract ... release thousands of bacilli during speech, coughing and sneezing. Are the released bacilli viable? Some authors think they are dead. This is still unproved because no culture or animal inoculation has been possible up till now. We should not worry too much because clinical experience has shown that the danger of leprosy transmission is in fact extremely small. Cases of close contact for years do not acquire leprosy. Bacilli in great masses reach healthy persons without leading to disease. We may however not conclude that bacilli released by the respiratory tract do not play a role in the transmission of leprosy".

It is probable that both Schäffer's patients on whom these experiments were done, besides having heavily infected nasal discharge, were also suffering from heavy involvement of the throat and larynx and possibly of the palate also. Such cases of untreated florid lepromatous leprosy are not easy to find in these days of treatment with DDS.

TRANSMISSION BY DROPLET INFECTION

Schäffer's findings on sneezing have been confirmed by Pedley and Geater (working in Bhutan). An untrated lepromatous patient whose noseblow smears were heavily infected with acid fast bacilli (including many globi), was made to sneeze at a barrier of adjacent slides set up at 20 cm. from the face. Two slides which had on them many specks of mucus were selected for examination. A total area of 39 square cm. on these two slides revealed the presence of 500 droplets of sizes varying from 0.2 mm. to 0.7 mm. in diameter. In 375 of these droplets (75%), acid fast bacilli occuring singly, and in globi formation were present (colour plate). Many of the bacilli were morphologically normal. Similar findings were made in slides set up at 30 cm. and 50 cm. from the face during sneezing (6). The slides from which the photomicrographs were taken are kept in the leprosy study Centre in London.

Recently, Rees and McDougall (6), published findings of a study which they undertook to determine whether mice were susceptible to airborne infection with *M. leprae*. This study consisted in exposing mice (with artificially depressed cell immunity) to *M. leprae* in aerosols for periods of 14 to 24 months. As the mice died or were killed, acid fast bacilli (with the characteristics of *M. leprae*) were harvested from one or more of the following sites: the ears, footpads, nose, bone-marrow (in one mouse at the end of 24 months), and lung. Evidence showed that the infection of these sites had arisen from systemic spread of bacilli initially entering the lungs.

TRANSMISSION BY HUMAN MILK

Pedley (7) has shown that it can be estimated that an infant being breast-fed by a mother with advanced, untreated lepromatous leprosy would ingest about 2 million bacilli in the course of one day. The finding of *M. leprae* in the mammary gland, in its lumina and their cell linings, in cases of lepromatous leprosy, has been well documented by photomicrography in other papers by Pedley (8, 9, 10). Perhaps it would be well to mention that this finding should not cause (on the child's account) undue alarm because:

(1) DDS treatment eliminates the bacilli from the breast milk in the course of a number of weeks, and

(2) The DDS is secreted in the milk one or two hours after it is taken by the mother. Thus the child will be getting it by mouth prophylactically, and should not be removed from the breast.

TRANSMISSION BY VECTORS*

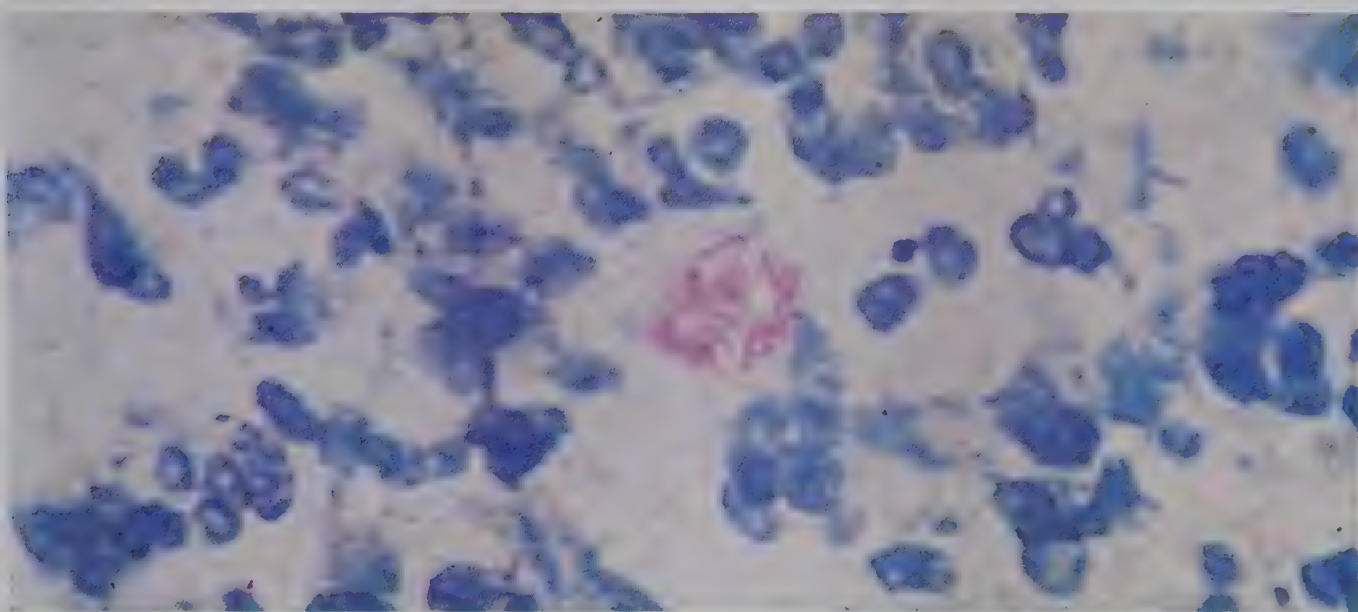
Kurian (11) reports that:

"Workers in JIPMER have been studying the role of insects in the transmission of leprosy from 1969.

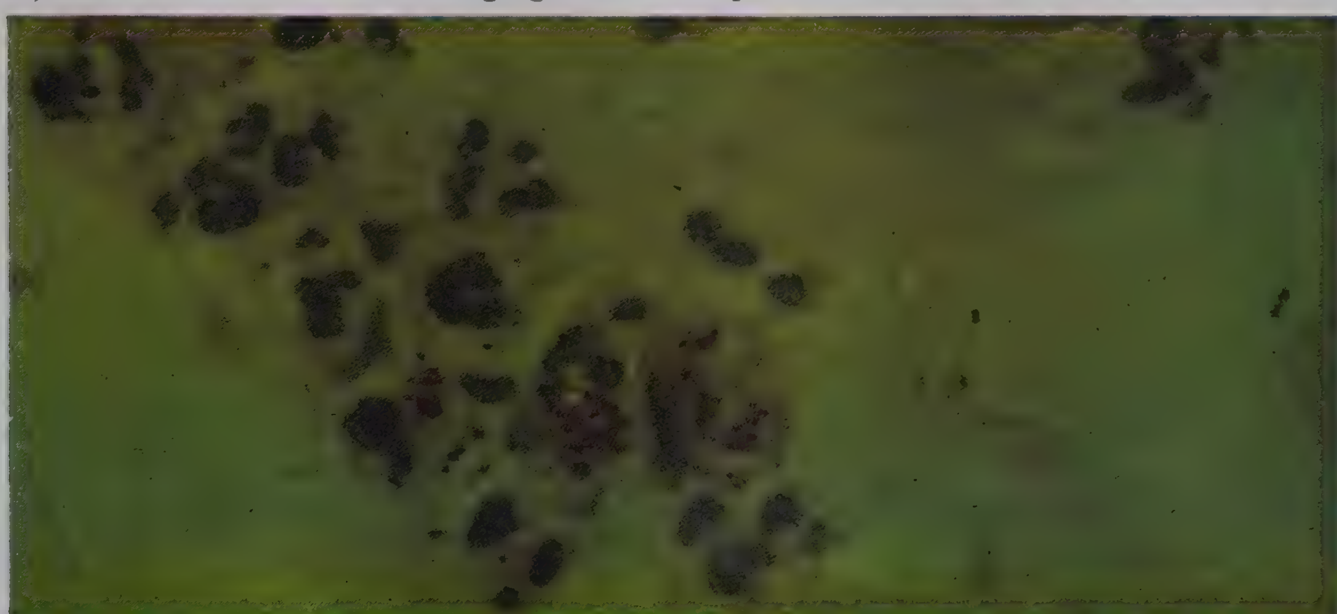
Mosquitoes, bedbugs, lice, ticks and itch mites were collected from patients (or their houses) suffering from lepromatous leprosy and injected into the foot-pads of mice. Two pools of Culex mosquitoes have yielded viable leprosy bacilli. Mosquitoes and bed-bugs reared in the laboratory were allowed to bite patients with untreated

(*The JIPMER, Pondicherry group have, in their latest report (Lep. in India, 1977:49:18-186), claimed foot pad infection of mice bitten on the pad by Aedes aegypti mosquitoes pre-fed on untreated lepromatous leprosy patients. According to the authors M. leprae were probably mechanically transferred with the proboscis, and did not invole any biological cycle in the arthropad-Editor.)

(a) Sneeze at 20 cm.



(b) Sneeze at 30 cm. Large globus in droplet.



(c) Sneeze at 50 cm.

Fig. 1
A study of 3 composite skin contact smears comprising 30 sq. cm of skin surface beneath which lay many bacilli— a fair proportion in solid staining rod form. Non-apparent lepromatous leprosy.

lepromatous leprosy. When these insects were killed and injected into mice, multiplication of leprosy bacilli was demonstrated, suggesting that blood sucking insects can transmit leprosy. This work requires further confirmation".

CONCLUSIONS

It is a great pity that for more than 70 years Schäffer's work was allowed to sink into oblivion. Now that animal innoculation is possible and has led to the knowledge that *M. leprae* can remain viable outside the human body for days, Schäffer's postulate that the disease could be transmitted by droplet infection is very significant. Perhaps if more heed had been paid to Schâffer's findings, the unproven hypothesis of transmission by skin to skin contact would not have met with such wide acceptance, which resulted in another fallacy, namely, that the BI of the skin-slit scrapes was the index of a patient's infectivity. We now know that this is not so, but rather the BI is:

(1) An index of the activity of the disease as reflected in the Morphological Index (MI).

(2) An indication of the speed with which the host can eliminate the bacillus from the tissues.

(3) A valuable means of detecting (by the MI) the appearance of dapsone-insensitive bacilli.

The only true index of infectivity is the presence of morphologically normal bacilli in the noseblow. THIS FREES ALL BORDERLINE AND TUBERCULOID PATIENTS FROM THE STIGMA OF INFECTIVITY, AND REDUCES THE PERIOD OF INFECTIVITY OF TREATED LEPROMATOUS PATIENTS TO A MATTER OF MONTHS.

A POSTULATE

It can now be postulated, in the light of modern knowledge that the most probable way by which leprosy is transmitted is by inhalation and ingestion. By inhalation, infected droplets could be carried direct to the alveolar spaces of the lung, whence they could enter the circulation.

However, it must not be forgotten that because the bronchial tree is lined with ciliated epithelium as far as the alveoli, and the beat of the cilia is UPWARDS, inhaled droplets could, by the action of the cilia, be returned up the bronchial tree to enter the oesophagus and so reach the stomach, which could also be a point of entry into the circulation. The nasal passages are also lined with ciliated epithelium whose action constantly keeps a covering film of mucus moving TOWARDS the naso-pharynz. Thus, infected droplets inhaled into the nasal passages are likely to be moved on, by the action of the cilia, to reach the nasopharynx and thence to be, either inhaled into the lung, or ingested into the stomach. If it is reasonable to believe that M. tuberculosis can pass through the mucosa of the stomach and so reach the lymph glands of the mesentery, it is not unreasonable to postulate that *M. leprae* could gain access to the circulation through the mucosa of the stomach and end up in nerve tissue and get taken up by the Schwann cells. Study of nerve tissue in leprosy seems to suggest that the leprosy bacillus can shelter in the Schwann cells for an indefinite period and even multiply in them. This suggests that the Schwann cell could, perhaps, play a significant role in the incubation period of the disease.

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INFECTIVITY OF LEPROSY

S. K. NOORDEEN

The term 'infectivity', in its strictly scientific sense, would refer to the occurrence of infection, with or without manifest disease, such infection being capable of identification through laboratory or other tests. However in a more restricted and popular application the term 'infectivity' may just confine itself to the occurrence of manifest infective disease. This will be particularly true in situations where identification of infection without manifest disease is rather difficult as in the case of leprosy. In this presentation whenever we refer to infectivity of leprosy it will only be with reference to occurrence of manifest disease.

Although we do not definitely know the exact mechanism of transmission of leprosy, we have more than enough evidence that the disease is more easily acquired by persons who are in close association with leprosy patients, particularly with patients who harbour large number of organisms. It is with reference to this observation that the early workers used the term 'contact' as a method of transmission in leprosy. However the definition of 'contact' by later workers with qualifications such as 'skin to skin', 'intimate', 'prolonged' etc. made it appear as if the disease could be acquired only through such methods, and that transmission involved some kind of 'inunction' of the organisms from the skin of affected persons to skin of healthy persons. The evidence in favour of transmission of leprosy exclusively through 'inunction' is becoming less and less definite.

The measurement of infectivity of leprosy under varying conditions has been carried out by several workers, particularly with reference to risk of disease for persons exposed to leprosy cases within the household. Such measurements expressed as 'attack rates' for contacts indicate that there is a great deal of variation, as seen from reports from various sources. However it should be understood that observed variations in attack rates among contacts are as often or more often due to methodological differences in the various studies as due to epidemiological factors. The methodological factors include—(i) frequency of follow-up observation; (ii) duration of follow-up, and (iii) criteria for diagnosis of early leprosy. The frequency of examination of contacts is an important factor which influences attack rates. This is mainly because of the early lesions showing a high tendency for spontaneous healing after varying periods of time. When the examinations are more frequent it is likely that more of the early lesions will be picked up which otherwise might escape notice due to spontaneous healing that might take place between examinations. The attack rates in such studies with frequent examinations are likely to be much higher as compared with studies where examinations are infrequent. Another methodological factor that influences attack rates is duration of follow-up. When values for attack rates per unit time are calculated in studies where duration of follow-up is long, the relatively higher attack rates of earlier periods of exposure get diluted by the low attack rates of later periods, whereas attack rates are likely to be higher in studies where duration of follow-up is short. The decline in attack rates in the same cohort with passage of time is partly due to the index cases becoming less and less infective as time passes, and partly due to the possibility of the more susceptible contacts developing the disease earlier leaving behind the more resistent ones. Lastly the critieria for diagnosis of early lesions and method of examinations may also influence attack rates. Studies which have stringent criteria for diagnosis may show lower attack rates than those where diagnosis is made on less definite grounds. Even where criteria for diagnosis are prefixed there are likely to be inter-observer variations, particularly in relation to early lesions among children.

The epidemiological factors that influence attack rates among contacts are many. They include factors related to the contacts as well as those related to the index (source) cases to which the contacts are exposed. The factors relating to the contacts are age, sex, prior exposure to other mycobacteria, relationship to the index cases, and possibly nutritional factors. The factors relating to the index cases include number of index cases in the household, type of leprosy, bacteriological state, treatment state, as well as age and sex of the index cases. In addition attack rates are also capable of being influenced by environmental factors including geographic factors. Some of the more important factors mentioned above are discussed below.

Age and Sex

Although it is well recognized that household contacts of leprosy patients run a higher risk of getting the disease, the extent of such risk under varying conditions is not fully understood. In a study at Chengalpattu Taluk of Tamilnadu State in the 1960's it was found that household contacts had a risk which was 4.8 times that of others who were not household contacts . This increased risk for contacts was 9.5 times where the index case was of lepromatous type and 3.7 times where it was non-lepromatous type. In other words the risk for contacts of lepromatous cases was 2.6 times that for contacts of non-lepromatous cases. These differential risks as brought out by the attack rates varied with age, as shown in Table-I.

Table-II shows the relative risks for household contacts of the two types as a ratio of risk to non-household contacts according to the three main age groups.

TABLE II

Relative Risk of getting leprosy for non-contacts and others by age group

Age group	Non-household contacts	Non-Lepromatous contacts	Lepromatous contacts
0-14	1	3.8	26.9
15-44	1	4.0	5.6
45+	1	3.6	3.6
Total all ages	1	3.7	9.5

It can be seen that the relative risk for contacts of Non-lepromatous cases, in relation to non-household contacts, is more or less constant for all ages, whereas there are wide variations in relative risks among the three age groups for contacts of lepromatous cases. It is also interesting to note that the increased risk for contacts of lepromatous cases is most pronounced in the age group 0-14. In the age group 15-44 the increased risk for contacts of lepromatous cases is only slightly more than that for the contacts of non-lepromatous cases. In the age group

TABLE I

Attack rates for contacts and others according to age

Age group	Non-household contacts			Household contacts of L cases			Household contacts of N cases		
	Number exposed	New cases in 5 years	Attack Rate per 1000 per year	Number exposed	New cases in 5 years	Attack Rate per 1000 per year	Number exposed	New cases in 5 years	Attack Rate per 1000 per year
0-14	70346	356	1.01	398	54	27.14	4835	92	3.81
15-44	82977	864	2.08	426	25	11.74	4652	195	8.38
45+	32724	503	3.07	201	11	10.95	1686	92	10.91
Total all ages	186047	1723	1.85	1025	90	17.56	11173	379	6.78

45 and over the contacts of lepromatous cases seem to run the same risk as contacts of non-lepromatous cases.

In general, under several situations, the risk of getting leprosy for females was less than that for males. This is shown in Table-III.

TABLE III

Attack Rates for contacts and others of various age groups by sex

Contact state and age group		MALE			FEMALE			Relative Risk for Males (with Female Rate as 1)
		Number exposed	New cases in 5 years	Attack Rate per 1000 per year	Number exposed	New cases in 5 years	Attack Rate per 1000 per year	
Non-household contacts	0-14	34642	188	1.09	35704	168	0.94	1.2
,, ,,	15-44	40831	599	2.93	42146	265	1.26	2.3
,, ,,	45+	17155	301	3.51	15569	202	2.59	1.4
,, ,,	all ages	92628	1088	2.35	93419	635	1.36	1.7
Household contacts	0-14	3111	114	7.33	3047	82	5.38	1.4
,, ,,	15-44	2727	195	14.30	3224	117	7.26	2.0
,, ,,	45+	1045	61	11.67	1121	65	11.60	1.0
,, ,,	all ages	6883	370	10.75	7392	260	7.03	1.5

The increased risk for males is about the same whether they are household contacts or others. Both among household contacts and others the increased risk is more marked in the age group 15-44. Among non-household contacts, the increased risk for males in the age group 0-14 was only slightly more than that for females. There was practically no sex difference among household contacts in the age group 45 and over.

Relationship of contacts to Index cases

Even within the household the risk of getting leprosy can vary with relationship of the contact to the index cases. The control group of contacts in the chemoprophylaxis studies of the Central Leprosy Institute carried out in 1970's in the Sriperumbudur Taluk of Tamilnadu State provided reliable information on this, as can be seen from Table-IV[2].

It can be seen that among various relationships, siblings appear to run comparatively greater risks. The chemoprophylaxis studies at Sriperumbudur Taluk did not show as marked a difference in attack rates between child contacts of lepromatous

TABLE IV

Attack Rates for contacts of L and N cases according to Relationship of contacts to index cases

Relationship of contacts to Index cases	Contacts of non-lepromatous cases			Contacts of lepromatous cases		
	Person-years of observation	New cases	Attack Rate per 1000 per year	Person-years of observation	New cases	Attack Rate per 1000 per year
Child	1252.7	46	36.72	366.1	19	51.90
Sibling	986.8	49	49.66	93.1	8	85.93
Other relationships (Grandchild, cousin etc.)	387.9	14	36.09	222.2	11	49.50
Total	2627.4	109	41.49	681.4	38	55.77

and non-lepromatous cases, as compared with results of earlier routine contact studies at Chengalpattu Taluk. This appears to be partly due to some unknown geographic or environmental difference between the two areas, and partly due to different methodologies for observations, follow-up etc. employed in the two areas. The follow-up etc. were much more intensive in the chemoprophylaxis studies of Sriperumbudur Taluk.

Geographic factors

Geographic differences in attack rates among household contacts of lepromatous cases have also been observed between areas studied concurrently using similar methodology. Table-V shows geographic differences in attack rate for household contacts of lepromatous cases in two parts of Sriperumbudur Taluk, as seen from the control groups of contacts in a chemoprophylaxis study.

TABLE V

Attack Rates for contacts of lepromatous cases in two adjacent areas studied concurrently.

Geographic Region	Person-years of observation	New cases	Attack Rate per 1000 per year
Northern part of Sriperumbudur Taluk	277.3	24	86.55
Southern Part of Sriperumbudur Taluk	404.2	14	34.64
Total	681.4	38	55.77

The data indicate that even under similar methods of observation two geographic areas even closeby can show different attack rates under conditions where comparable contacts are exposed to comparable index cases for comparable periods. This suggests that exposure of contacts to index cases in the household is not the sole deciding factor in the transmission of leprosy, and that other unknown factors may also be equally important.

Bacteriological state of Index cases

Bacteriological state of index cases of lepromatous type is one of the factors concerning index cases that influence attack rates among contacts. This was brought out through attack rates observed among contacts kept as controls in two different studies on chemoprophylaxis carried out by the Central Leprosy Institute [2,3]. This is shown in Table-VI.

Number of index cases in the households

Another factor which influences attack rates among contacts is the number of index cases in the households where they live. This was observed in a routine contact survey covering contacts of index cases of all types in Chengalpattu Taluk, as well as among contacts of non-lepromatous cases kept as controls in a chemoprophylaxis study. This is shown in Table-VII, and Table-VIII.

The infectivity of leprosy is thus influenced by several factors. In addition to the known factors discussed above there may be several unknown factors that influence infectivity. For instance we have very little information on the role of 'carriers' in transmission of leprosy, although there is some evidence

TABLE VI

Attack Rates by bacteriological state of Index lepromatous cases in two chemoprophylaxis studies

Initial Bacteriological state	Chemoprophylaxis Study I			Chemoprophylaxis Study II		
	Person-years of observation	New cases	Attack Rate per 1000 per year	Person-years of observation	New cases	Attack Rate per 1000 per year
Negative	393.5	7	17.79	234.6	8	34.10
Positive	848.8	41	48.30	446.8	30	67.14
Total	1242.3	48	38.64	681.4	38	55.77

on the occurrence of acid fast organisms on the skin of apparently healthy individuals in leprosy endemic areas[4]. So also there is no reliable information available on the infectivity of lepromatous leprosy patients whose skin smears show no morphologically intact organisms. Lastly the role of possible extra human reservoirs of infection also cannot be ignored. Apart from studying infectivity through occurrence of new cases, the need for a specific and simple test for identifying infection in individuals in the absence of manifest disease cannot be over-emphasised. Until then it is not possible to fill several important gaps in the knowledge on epidemiology of leprosy.

TABLE VII

Attack Rates among contacts of all types by number of index cases

Number of index cases	Number of contacts exposed	New cases in 22 months	Attack Rate per 1000 per year
One	12198	172	7.7
Two	1665	48	15.7
Three	329	9	14.9
Four or more	83	4	26.3
Total	14275	233	8.9

TABLE VIII

Attack Rates among contacts of non-lepromatous cases by number of index cases

Number of Index cases	Person-years of observation	New cases	Attack Rate per 1000 per year
One or Two	2560.8	104	40.61
Three or more	66.7	5	74.96
Total	2627.4	109	41.49

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THE USE AND LIMITATIONS OF EPIDEMIOMETRIC MODELS IN LEPROSY

M. F. LECHAT, C. VELLUT, C. B. MISSON

Epidemiometric models in leprosy have a number of applications. They can serve to predict and simulate trends in the disease under different epidemiological conditions. They can be used to experiment with various control methods, including hypothetical methods not yet developed. The cost and effectiveness of possible strategies can also be evaluated by introducing economic parameters into the model.

The purpose of this paper is to review the information so far contributed to leprosy control by such models, to discuss further applications, and to determine conditions for their general applicability.

The model considered here has been described previously. It was developed using the data collected in the Polambakkam, Tamil Nadu, control scheme from 1955 to 1970.

Prediction of epidemiological trends.

For the last 25 years leprosy control in most areas of the world has been based on identifying as many cases as possible, following early detection of cases by mass treatment with sulphone drugs. Since the patients, especially those with positive bacteriology, are considered as the sole reservoir of the disease, it is assumed that the blanket treatment of patients with bacteriostatic drugs will progressively reduce transmission of the disease.

When sulphone drugs, especially DDS, were first introduced for leprosy control, much was expected of them. Complete eradication of leprosy, that is interruption of transmission and no subsequent new cases, was even seen as a realisable goal.

These high expectations have been followed by some disillusionment. Reported results vary greatly. While some countries claim a remarkable reduction in the number of cases detected or total cases treated, others are still registering a large number of new patients after 20 years of properly conducted leprosy control activities. While discrepancies can be attributed in part to the different indices used to assess the effectiveness of control activities (largely a confusion of true incidence with case-detection rates) this cannot explain all the differences. It should be stressed that incidence, i.e. the number of new cases in a given period (usually one year) in a given population, is the only valid measurement of transmission. The detection rate may include both new cases and prior cases, only recently detected ; thus it merely reflects the intensity of case-finding. In this respect, it is as much a yardstick of the development of health services or the changing extent of concern over leprosy as it is a measurement of transmission.

No large-scale, controlled studies have been conducted on the effectiveness of present leprosy strategies, since valid incidence data on a closely observed population are difficult to secure over long periods. There is therefore a lack of base line data which could be extrapoled in order to predict future trends. However, by defining the infective capacity of each class of patient (eight in all) according to type of leprosy, detection status, duration of therapy, and continuity of treatment, together with a given set of latency periods for each of the clinical types, the model has made possible the study of incidence as a dependant function of prevalence over the preceding years. That is, given prevalence figures over a number of years for each of the eight infective classes, incidence can be predicted for all successive years (Table 1).

Table 1.

ESTIMATES OF INFECTIVE CAPACITY IN VARIOUS CLASSES OF PATIENT IN THE MODEL.

State I		Infective capacity $d_I \times 100$
11	L. Untreated	44,63
12 A	L. Treated less than one year	44,71
12 B	L. Treated one year or more	0,98
13	L. Treatment interrupted	27,56
21	T. Untreated	13,38
22 A	T. Treated less than one year	13,41
22 B	T. Treated one year or more	0,26
23	T. Treatment interrupted	8,19

In the epidemiological context of Polambakkam, the model has shown that, using current control methods, it takes 14 years to reduce incidence by 50 per cent (Fig. 1). This clearly shows that the planning of leprosy control should be seen as a long term activity. Public health officials, international agencies and non-governmental organizations should be made aware that present methods of leprosy control are effective and that, providing the epidemiological conditions remain similar, considerable reduction in the leprosy problem can be expected. To achieve this long term investment, however, continued support and sustained effort are required.

There is, nevertheless, a dark side to the predictions made on the basis of the Polambakkam data. The analysis of bacteriological conversion rates according to length of treatment shows that the probability of a patient becoming negative tends to reach an asymptotic limit after 8 years (Fig. 2). This strongly suggests that sulphone-resistance is operating. If such is the case, incidence predictions should be revised upwards.

It is tempting to use the model to predict the effect drug resistance could have on future incidence. Simulations are currently being carried out to discover the effect that the development of secondary resistance according to various lengths of treatment (the annual attack rates for resistance, specific to length of treatment) would have on long-term incidence rates. Although results are not yet available preliminary tests suggest that incidence could be highly sensitive to sulphone-resistance. In other words, a small increase in the prevalence of secondary resistance could have dramatic consequences and possibly jeopardize the future of leprosy control.

Simulation of control methods

The effect of a number of control measures, available or still in the developmental stages, have been simulated by appropriate modifications to the parameters of the model. Incidence under each method was compared over a 20 year period. The following control methods were considered :

— Unmodified leprosy control, as carried out at present in the study population, based on early detection and regular treatment.

— Vaccination with a BCG form of type-specific vaccine, 100% effective in preventing the development of the lepromatous type of leprosy and converting potential lepromatous cases into tuberculoids.

— Vaccination with a disease-specific vaccine, 100% effective in preventing leprosy.

— Improvement over present conditions for ensuring patients' continuity of treatment.

— Isolation of lepromatous patients for one year after detection.

It appears that, under the conditions of the model, the most effective method by far for controlling leprosy in the long-term would be vaccination with a leprosy specific vaccine, should it become available. With such a 100% effective vaccine, administered to 100 per cent of the population, incidence would be reduced to 0.25 per 10.000 after 10 years (Fig. 1).

The comparison of segregation and specific vaccination is particularly striking. Specific vaccination of only 20 per cent of the population, plus babies over subsequent years, is as effective in controlling the disease, after 10 years, as the isolation of all new, bacteriologically positive patients for one year after

FIG.1. PREDICTION OF INCIDENCE (TOTAL NEW CASES) FOR THE CURRENT METHOD AND FOUR SIMULATED STRATEGIES

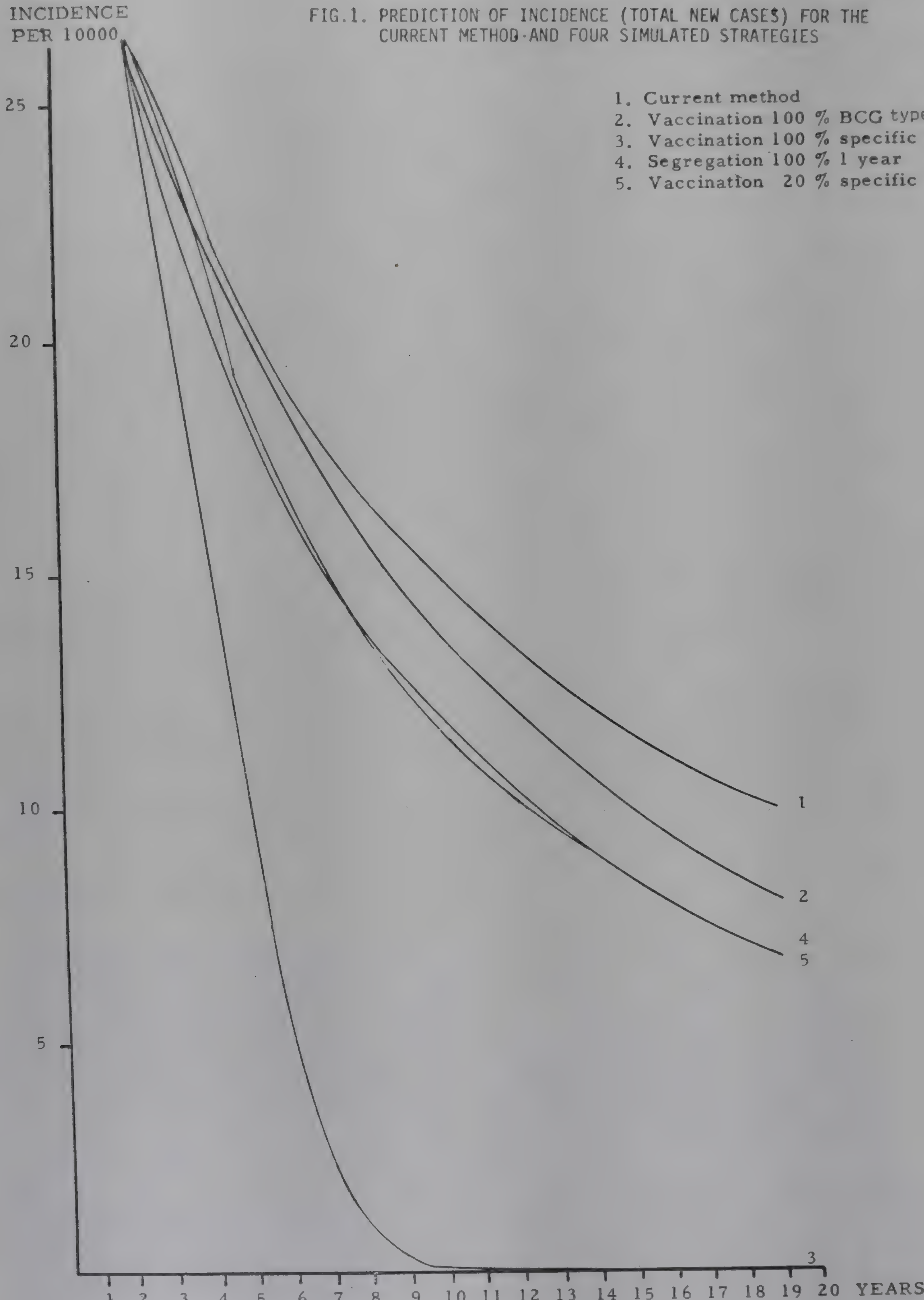
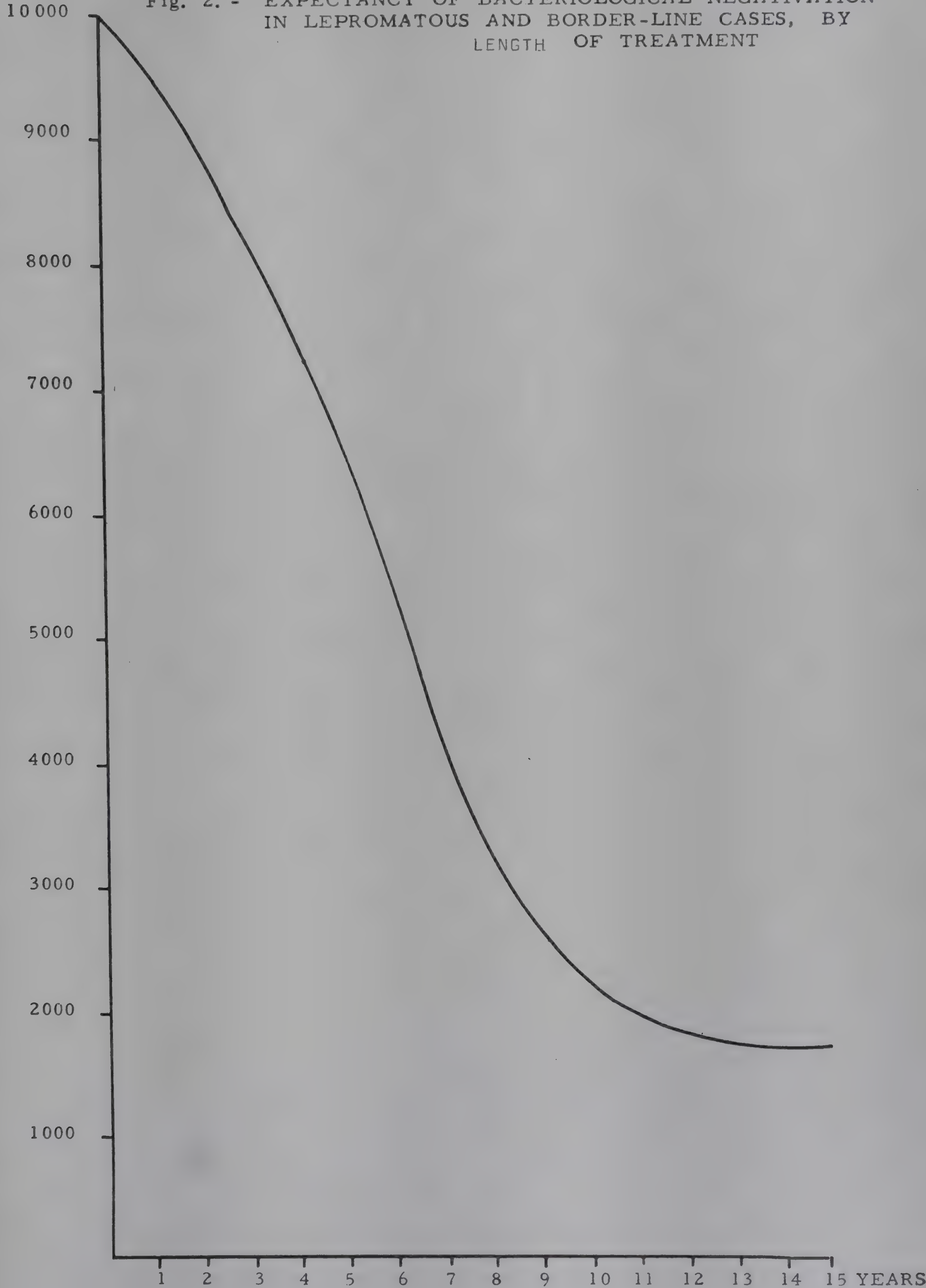


Fig. 2. - EXPECTANCY OF BACTERIOLOGICAL NEGATIVATION IN LEPROMATOUS AND BORDER-LINE CASES, BY LENGTH OF TREATMENT



detection (Fig. 1). In terms of cost, the two measures differ by an estimated factor of 2.23.

Segregation appears far less effective in spite of its very high cost. Temporary segregation of all new, bacteriologically positive patients for one year after detection brings a 74.7 per cent reduction of incidence after 20 years as compared with 61.7 under present measures.

The BCG type vaccination which was simulated was assumed capable of inducing a non-bacteriologically positive type of leprosy in patient who would otherwise have developed a bacteriologically positive form of the disease (lepromatous or border-line). At one time, great hopes rested on such a means of prevention, since it is assumed that these bacteriologically negative patients play either a minimal role or no part at all in transmission of the disease. The model has, however, shown that the role of such a non-specific vaccine in reducing transmission of the disease is likely to be negligible (Fig. 1).

In order to investigate this rather paradoxical result, simulations have been carried out in which bacteriologically positive patients have been written off altogether. We could, for example imagine a situation where strict enforcement of segregation is implemented from the moment of onset of the disease for life, with no possibility whatever of transmission (these conditions for transmission are in fact the same as those for death). In such conditions, only slightly or non-infective patients could ensure transmission. In the model, infective capacity for each class of patient has been measured as the number of people infected by one patient in one year (Table 1). These parameters have been deducted from data collected in the Polambakkam area, using a method of least squares minimization which has been described elsewhere. Estimates are consistent with the observations made by Doull and Guinto in the Philippines, who concluded that attack-rates were four times higher (6.2 per 1000 person-years of observation) in lepromatous than in non-lepromatous patients (1.6 per 1000 person-years of observation) as compared with 0.8 in cases who had no home contact.

However, predictions from the model indicate that even with no lepromatous cases present, incidence will still reach 4 per 10,000 after 20 years (Fig. 3). This suggests that tuberculoid patients, even if they only represent a negligible hazard on an individual contact basis, could still, as a whole, constitute a significant reservoir for transmission, due solely to their large numbers. This observation could be important in countries where non-lepromatous patients make up a large proportion, up to 95 per cent, of the total number of cases. Possibly, the usual recommendation, that in cases of budgetary limitation treatment is to be preferentially reserved for bacteriologically positive cases, should be reconsidered in the light of these results.

However, no vaccination is available as yet, and segregation can be ruled out as relatively inefficient, especially in view of its considerable cost. Thus the most effective method of control appears from the model to be improved case-holding, in other words, a reduction in the rate of patients abandonning treatment. This could presumably be achieved through appropriate health education and community participation.

A 50% improvement in case-holding as defined in the model, brings a 4% reduction in incidence as compared with current measures. Ultimately, however, improvement of case-holding is only a minimalist's answer. Even if no patients at all are allowed to abandon treatment, a Utopian objective, incidence reduction after 20 years will be only 64.9% as against 61.7% with the current method. Its use should therefore be balanced against its cost.

In terms of research, there is no doubt that the development of a specific vaccine constitutes the highest priority for leprosy research today. The model shows clearly that this is the only method which could bring incidence to zero within one generation. This fact justifies current efforts to promote and coordinate research in to the microbiology and immunology of leprosy, especially in connection with the WHO Special Programme for Research and Training in Tropical Diseases.

There are other potential simulations which could yield important information. One which comes immediately to mind is simulating the use of combined therapy and second line drugs for preventing or circumventing drug resistance. The model could for example be used to predict the effect of fast acting drugs such as rifampicind on long-term incidence. This, however, would require estimates of the appropriate rates for relapses

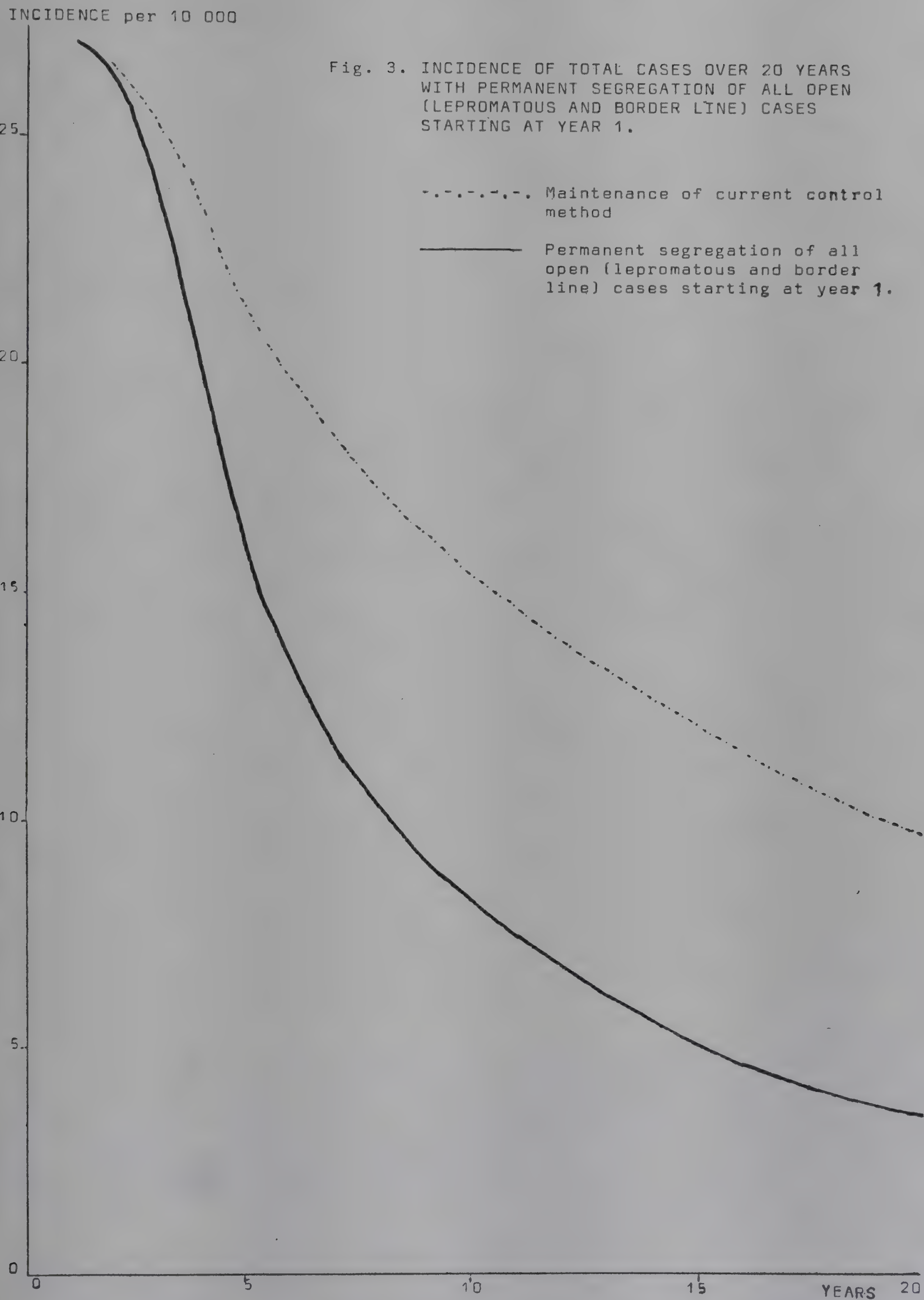


Fig. 3. INCIDENCE OF TOTAL CASES OVER 20 YEARS WITH PERMANENT SEGREGATION OF ALL OPEN (LEPROMATOUS AND BORDER LINE) CASES STARTING AT YEAR 1.

following treatment with non-sulphone drugs, and these are still not available at present. Up to now this lack has prevented the use of the model to explore this crucial aspect of tomorrow's leprosy control.

General applicability of the model

In its present state, the model can be used to predict long term trends for leprosy in the study population, and to simulate the effects of various control measures.

To what extent it can be applied to other populations is open to discussion. Its general applicability depends on whether the estimated parameters for infective capacity in each class of patient and the distribution of latency periods are valid for other populations. This can only be determined by tests in other areas, where various epidemiological features on which the current model is presumably dependent are present.

These features are : (1) the prevalence of leprosy should not be too different from prevalence in Polambakkam, that is it should be of the same order of magnitude, since at low prevalence levels the chances of contact with infective patients are expected to decrease rapidly ; (2) the population should mix randomly in such a way that all susceptible individuals have a reasonably similar risk of exposure to a source of infection, (this implies no social or geographical clustering) ; (3) migration rates for latent cases should be balanced at the interface between the study area and the surrounding area, in such a way that the number of patients infected outside the area and developing the disease inside it should compensate for the number of patients infected inside the area and developing the disease outside it.

Such tests would also depend on the availability of valid statistical records from which to derive the basic epidemiological indices and parameters.

It is hoped that validation of the model in suitable areas will help in the design of appropriate strategies for leprosy control and will assist in long-term planning.

GENETICS IN LEPROSY

BERNARDO BEIGUELMAN

The hypothesis of hereditary transmission of leprosy, supported by eminent authorities in the past (Danielssen and Boeck, 1848), was rapidly forsaken when Hansen recognized *Mycobacterium leprae* as the pathogenic agent of this disease. Nevertheless, at no moment it was put into doubt that leprosy manifestations, like any other chronic or acute infectious disease, depend upon the degree of susceptibility of Man to the development of its pathogenic agent. As a matter of fact, it is a principle of general pathology that three components should always be taken into account when an infectious disease is under consideration: the pathogenic agent, the degree of host resistance and the environmental conditions.

In the particular case of leprosy it is accepted beyond doubt that the degree of tissular resistance of Man to the development of *M. leprae* plays a prominent role among the factors which interfere in the manifestation of this disease. In this context mention should be made of the large number of unsuccessful trials made in the last century by Danielssen, Profeta and Mouritz (*cf.* Alonso, 1966) to provoke leprosy manifestation in experiments made in *anima nobile,* as well as the descriptions of tuberculoid lesions after accidental inoculations of leprosy bacilli. Among them, the most known are the papers of Porrit and Olsen (1947) and Aguas (1967). The former was concerned to two American soldiers who exhibited tuberculoid lesions in their tatoos made three years before, at the same day, by the same professional. The latter reported the occurrence of tuberculoid leprosy in a pair of twins who received three blood transfusions from a lepromatous donor.

Since no phenotypic manifestation can be supposed without the commitment of some genetic entity, it seems obvious that resistance or susceptibility to an infection shall depend, in a higher or lesser degree, upon inherited factors of the host. It is therefore surprising that interest on genetic research on leprosy has begun only in the last decade, twenty years after a period of intensive speculations on this subject (Rotberg, 1937; Tolen tino, 1938; Aycock and McKinley, 1938; Aycock, 1940).

The investigations of evaluating whether or not the genetic constitution of Man plays an important role in determining resistance or susceptibility to leprosy manifestation pursued different research lines and will be summarized in the present paper.

1. Studies on familial recurrence of leprosy

A non-random familial recurrence of a communicable disease may not be observed in areas where its prevalence values are high. In spite of leprosy being always considered as a familial disease, no clear demonstrations were given until 1968 of its non-random recurrence in families living in an endemic area where leprosy cases were frequently observed (Beiguelman, Dall'Aglio and Da Silva, 1968_a). Of course, such a demonstration does not mean too much for genetic purposes, since differential exposure conditions can not be ruled out even in this case. Nevertheless, though not sufficient, familial association is a necessary condition for supposing that some important inherited component of the host is involved in leprosy manifestations.

2. Studies on familial association of leprosy forms

Informations on familial association of leprosy forms were drawn from an investiga-

tion of concordance of polar types of leprosy among sib pairs (Beiguelman, Dall'Aglio and Da Silva, 1968). Polar types of leprosy were chosen for study because of their stability. The sib method was employed because random samples of sib pairs disclose greater genetic and environmental similarities, or smaller ages differences, than any other pairs of consanguineous relatives except twins. In this investigation a significant excess of sib pairs concordant for the lepromatous and the tuberculoid types of leprosy was observed.

If the epidemiological principle that affected individuals derived from the same *focus* are a consequence of infection by the same strain of bacilli is accepted as true then these data may be considered to indicate that the association observed depends upon genetic variations of the host rather than of *M. leprae*. This suggestion is favoured by the observation that except for one of 111 sib pairs examined by Beiguelman, Dall'Aglio and Da Silva (1968) a common *focus* to each pair was recognized. Moreover, 31.8% of the concordant pairs have shown signs of leprosy practically at the same time.

Discordant results published in pertinent literature (Horton and Povey, 1966; Rao, Karat and Karat, 1969) are not comparable. Thus, Horton and Povey (1966), who analysed multiple-case families, included borderline and indeterminate patients in a single class and considered all first-grade relatives for comparison. Concerning Rao, Karat and Karat's (1969) paper it should be remembered they have emphasized that the concept of family they adopted is divorced from genetic significance, because they defined family as "a group of individuals partaking food from a common kitchen".

3. Studies on intrafamilial contagion of leprosy

A great number of surveys on the contagion of spouses of leprosy patients has been published to point out the low contagiousness of leprosy, and to use this fact to suggest that susceptibility to this disease is under the influence of important inherited factors. For reference see, for instance, Quagliato (1957) and Mohamed-Ali (1965_a).

It seems obvious that a better argument in this direction would be provided by the demonstration that the attack-rate of leprosy is proportional to the coefficient of relationship of the contacts to the infectious index-case. Since time of cohabitation may be associated to the coefficient of relationship, it seems also clear that this difficulty should be circumvented by special methodology. Unfortunately, the papers dealing with this problem are concerned to inquiries of samples of contacts who became affected, for verifying their relationship to presumed *foci*, and did not take into account the leprosy form of either the affected contacts or the index-cases (Spickett, 1962_a; Mohamed-Ali, 1965_b).

We have analysed this question partially by studying the intrafamilial contagion rate of leprosy (Beiguelman, 1971_a). For this purpose complete families were investigated in which the father, the mother or both parents were lepromatous patients, as well as couples including a lepromatous partner. In both situations the relatives had at least five years of cohabitation with the lepromatous *focus*. This restriction was adopted because, according to Quagliato's data, 95% of the individuals who become affected by leprosy when married to a lepromatous partner manifest the first signs of this disease during the first five years of cohabitation. During the first three years only 44% of them show these signs (Quagliato, 1957).

Our data on intrafamilial contagion of leprosy is summarized in table 1 and makes evident that the consanguinous relatives of lepromatous cases are proner to exhibit the same type of leprosy than non-consanguinous relatives (spouses). The same data serves to show that in the offspring of couples composed of one affected partner, the frequency of lepromatous individuals is independent of the sex of the lepromatous parent. The higher frequency of lepromatous cases in the offspring of families with both parents lepromatous can not be used as an argument favouring the importance of inherited factors of Man for determining susceptibility to leprosy, because we can not exclude the environmental influences. Nevertheless, taken as a whole the data on table 1 may be considered as strongly suggestive of the importance of those factors.

The data on table 1 is also useful to point out the need for distinguishing the clinical forms of leprosy in such kind of investigation, and to emphasize that failure in discriminating leprosy forms may be responsible for controversial results.

TABLE 1

INTRAFAMILIAL CONTAGION RATE

Lepromatous Focus	Contacts Examined	Contagion Rate (%)				
		Lepromatous	Tuberculoid	Indeterminate	Borderline	Total
Father (167)	Son (346)	11.0	1.2	4.9	0.3	17.4
	Daughter (334)	7.5	1.8	3.0	—	12.3
	Both (680)	9.3	1.4	4.0	0.2	14.9
Mother (92)	Son (180)	11.1	1.7	3.9	—	16.7
	Daughter (176)	7.4	2.2	5.1	—	14.7
	Both (356)	9.3	1.9	4.5	—	15.7
Both parents (30)	Son (74)	25.7	5.4	8.1	—	39.2
	Daughter (55)	20.0	1.8	1.8	—	23.6
	Both (129)	23.2	3.8	5.4	—	32.4
Husband (271)	Wife (271)	2.9	6.3	3.7	—	12.9
Wife (159)	Husband (159)	5.7	5.0	3.1	—	13.8
Spouse (430)	Spouse (430)	4.0	5.8	3.5	—	13.3

4. **Population studies**

Some epidemiological data reveals that the lepromatous rates in highly endemic areas never surpass 5 to 10 per 1,000, even when leprosy prevalence is larger than 20 per 1,000 (Doull *et al.,* 1942; Fonte, 1967). Other data show that the proportion of lepromatous cases decreases as the prevalence of leprosy increases (Kapoor, 1963; Bechelli, Martinez-Dominguez and Patwary, 1966), with lepromatous rate tending to remain apparently stable in highly endemic areas.

While these observations may suggest that susceptibility to lepromatous leprosy depends upon an important genetic component of Man, they indicate that genetic interpretation ascribed to racial differences on leprosy prevalence (Spickett, 1962 $_{a,b}$) isopen to criticism. Since leprosy prevalence depends on both the existence of open cases and the opportunity of exposure to infection by *M. leprae,* even the arguments based on surveys in multiracial communities may be questioned. Among them, only the climate is a non-genetic variable which can be always minimized.

The above observations serve also to support the hypothesis that the comparisons of the distribution of leprosy forms in different populations may have no meaning for drawing genetic conclusions. For instance, the statement that European and Mongoloids are proner to manifest the lepromatous type of leprosy than Indians and Africans (Cochrane, 1947) may be a consequence of biased information, since small prevalence values are associated to large lepromatous prevalence figures, and *vice-versa.*

Concerning the studies of genetic isolates it should be emphasized that they are very useful to investigate constitutional diseases. Thus, if a rare inborn disease occurs more frequently in an isolate than in the general population, the hypothesis that it is inherited recessively will be favoured, because isolates exhibit higher consanguinity rates than non-isolated populations. The same statement can not be applied to infectious diseases if it is not demonstrated that isolated and non-isolated groups are under the same environmental influence or that they are racially and socially similar. For example, the comparison of the isolate of German origin living in Colonia Tovar, Venezuela (Convit, Gonzales and Rassi, 1952) to the native populations can not be used to draw genetic conclusions.

Even when it is proved that leprosy prevalence is higher in the consanguinous than in the non-consanguinous fraction of an isolate, it may be argued that the consanguinity associated to the leprosy fraction of the isolate may be an effect rather than the cause of the disease. At any rate, it seems worthwhile to mention that the frequency of consanguinous

marriages among parents of lepromatous or tuberculoid patients from the State of Sao Paulo, Brazil did not differ from that observed in the general population (Beiguelman, 1962_b).

5. Twin pair studies

Twin pair studies can afford a powerful test for investigating whether or not a genetic component of Man plays an important role in determining susceptibility to leprosy. However, taking into account that leprosy infection may be manifested through different clinical expressions, it seems obvious that in these studies one can not simply compare the proportion of concordance for leprosy exhibited by monozygotic (MZ) and dizygotic (DZ) twin pairs. Further criteria should be considered in sampling twin pairs for this type of investigation to avoid biased and/or inconclusive results.

The first criterion that should be taken into consideration is that both MZ and DZ pairs should have had the same opportunity of exposition to *M. leprae*. To follow this criterion it seems that the best way is to ascertain twins starting from leprosy cases who offer or offered a high contagion risk.

Since leprosy is more frequent among males, at least in age-groups over 14 years (Doull *et al.,* 1942; Bechelli *et al.,* 1966, 1970; Beiguelman, Da Silva and Dall'Aglio, 1968) the second criterion that should be followed is to compare male and female MZ and DZ pairs separately and to disregard unlike-sex DZ twins.

A third criterion of utmost importance is concerned to the need of collecting twin pairs composed strictly by informative cases with respect to concordance or discordance for leprosy manifestations. Pairs including at least an indeterminate or borderline case can not be considered as informative for this purpose, because the concordance or discordance observed among them may be spurious, as a consequence of the instability of the indeterminate and borderline groups. Moreover, the indeterminate cases present usually a low bacilloscopic index and offer a low contagion risk.

Pairs composed of tuberculoid twins should also not be included because of either their low bacilloscopic index or the bias they may provoke. Thus, since lesions of tuberculoid leprosy may be missed, sporadic cases are less frequently detected than those occurring in families that include more than one leprous individual. Therefore, due to sampling conditions, an excess of these concordant pairs either among MZ or DZ twins may distort the conclusions in any direction. Furthermore, this distortion would be impossible to be evaluated. Even the tuberculoid-in-re action twins can not be considered as index-cases, in spite of the high bacteriologic index they may have. According to Bechelli and Guinto (1970), some of these patients may become bacteriologically negative without treatment.

At this point it seems clear that for this type of study the twin pairs should be ascertained starting from lepromatous cases who have a like-sex co-twin affected with the lepromatous or tuberculoid type of leprosy. Healthy co-twins of lepromatous patients may also be considered as informative when cohabiting with them for more than five years after the beginning of the disease in the latter. The inclusion of these pairs should also depend on the degree of severity of the disease presented by the affected co-twin and the regularity of the treatment. Either the severity of lepromatous leprosy or the regularity of treatment may be classified as recommended by Quagliato, Bechelli and Marques (1970) and the determination of zygosity may be made according to our recommendations (Beiguelman, 1971). A standard card for collecting data on twin pairs for leprosy studies has been proposed elsewhere (Beiguelman, 1974).

It seems obvious that detailed clinical examination, as well as bacilloscopic, immunological (Mitsuda reaction, at least) and histopathological data are of crucial importance in this type of study. Among other objectives, such documentation can help, in some cases, to decide whether a twin pair apparently discordant for leprosy manifestation includes, indeed, a tuberculoid co-twin, or it should be discarded from the sample because the latter belongs to the indeterminate group.

Unfortunately, twin pair studies for investigating how important is genetic variability of Man in determining susceptibility to leprosy are scarce and have not taken into consideration all the criteria mentioned above (Spickett, 1962_b; Mohamed-Ali, 1965_b; Mohamed-Ali and Ramanujam, 1966; Chakravartti and Vogel, 1973). A re-evaluation of the laborious studies of Mohamed-Ali and

Ramanujam (1966) and Chakravartti and Vogel (1973) would be, therefore, highly considered.

At any rate, the results published on this subject are not in oposition to the hypothesis of the existence of an important genetic component of Man responsible for leprosy manifestations.

6. Family and twin pair studies on Mitsuda reaction

Taking into account the indisputable importance of the late lepromin reaction (Mitsuda reaction) for prognostic purposes, it was also used as an approach to genetic studies on leprosy.

The Mitsuda reaction has proved to be a familial trait either in samples free of leprosy (Beiguelman, 1962_b, 1971_a; Beiguelman and Quagliato, 1965) or in a sample including families with at least a parent affected with a polar type of this disease (Beiguelman, 1965). From these studies it may be concluded that the Mitsuda reaction in the offspring generation is associated to that presented by the parental generation. Nevertheless, the monogenic interpretation offered in one of these papers (Beiguelman, 1965) shall be considered with caution, because of the postulates and the secondary hypothesis involved (Beiguelman, 1967).

A quantitative analysis of the Mitsuda reaction was made in a random sample of healthy twin pairs, non-contacts of leprosy cases, who were collected in elementary schools of Campinas, SP, Brazil (Beiguelman, 1971_a). Since the intraclass correlation coefficients presented by MZ and DZ pairs have not differed significantly, this result could, perhaps, be accepted as favouring the hypothesis that the Mitsuda reaction depends mainly upon environmental factors.

Nevertheless, if some other facts reviewed elsewhere (Beiguelman, 1971_a, 1972) concerned to Mitsuda reaction among leprous and healthy individuals are taken into consideration, another alternative hypothesis can not be ruled out. This hypothesis states that Mitsuda reaction might be an inherited trait, but that its expression among genetically lepromin positive individuals would depend mainly upon environmental agents.

For a better understanding of this hypothesis let us consider that a positive Mitsuda reaction depends upon both the ability of the macrophages to destroy phagocytized leprosy bacilli and the influence of sensitizing agents, represented by specific (*M. leprae*), paraspecific (other mycobacteria) and broad-specific stimuli (non-mycobacterial intracellular parasites). Let us also admit that only a small fraction of healthy populations has macrophages permanently and genetically unable to lyse phagocytized *M. leprae*. If this trait would be rare, then, the healthy twins randomly collected would be composed mostly by concordant pairs for this lysing ability of the macrophages, irrespectively of being MZ or DZ. Otherwise stated, most of the pairs would be composed of individuals genetically endowed to exhibit positive Mitsuda reaction, which would be clinically expressed or not on the dependance of environmental influences. Thus, in spite of Mitsuda reaction being an inherited trait, twin pairs randomly collected among healthy individuals could not disclose a higher intraclass correlation among MZ than among DZ pairs.

Light on this subject might be thrown by studies on the lepromin reaction clinically and histologically analysed in a sample of like-sex twins ascertained by starting from lepromatous index-cases. In such series the source of errors would be strongly reduced because all the pairs would include a co-twin exhibiting an undoubtedly negative Mitsuda reaction (index-case) and a co-twin (affected or healthy) intensively submitted to specific sensitizing stimuli. The twin pairs collected by Chakravartti and Vogel (1973) offer an excellent opportunity to this investigation.

7. Reaction of blood macrophages to killed leprosy bacilli

Thirty years after Benewolenskaja (1932) reported the *in vitro* phagocytosis of leprosy bacilli by blood macrophages, the studies on this subject were retaken with the purpose of obtaining a better clue to investigate both the mechanism of the Mitsuda reaction and the participation of hereditary factors on resistance to leprosy (Treo and Silva, 1963; Beiguelman and Barbieri, 1965; Barbieri and Correa, 1967; Beiguelman, 1968, 1971_c, 1972; Godal and Rees, 1970; Pisani, Beiguelman and Opromolla, 1973).

Some of the techniques used to analyse the *in vitro* reaction of blood macrophages against killed leprosy bacilli gave hopeful results concerning the study of macrophage function of leprosy patients (Beiguelman, 1972; Pisani, Beiguelman and Opromolla, 1973). However, the alleged correspondance between the Mitsuda reaction and this *in*

vitro test among healthy individuals could not be confirmed by Pisani, Beiguelman and Opromolla (1973), who showed that this test is not suitable for genetic investigation. As a matter of fact, the blood derived macrophages of healthy individuals exhibit either an incapacity or a low rate of *in vitro* phagocytosis and lysis of *M. leprae,* irrespective of these persons being contacts or not of leprosy patients or of the intensity of their Mitsuda reaction.

8. Pedigree studies

The fact that leprosy tends to cluster in families has stimulated some authors to apply formal genetics methods to genealogical data (Spickett, 1962_a; Prasad and Mohamed-Ali, 1966_b). However, pedigree analysis, which provide good results for rare constitutional diseases and not as good results for degenerative diseases, are not suitable for infectious diseases. As a matter of fact, the reliability of this method depends upon the high degree of minimization that can be attributed to the environmental influences on the trait under study.

In the particular case of leprosy it should be remembered that:

1. Affected individuals can not be considered as belonging to a single clinical entity, since leprosy is not a monomorphic disease.

2. Families with lepromatous or borderline patients are not comparable to those in which the leprosy cases are represented by tuberculoid or indeterminate individuals. The intrafamilial contagion-risk to which they are submitted is obviously strictly different.

3. Some factors which promote differential exposure to leprosy infection can not be ignored. Among them it seems important to consider the influence of extrafamilial *foci* living or not in the same household; period of cohabitation or frequency of exposure of the contact(s) and the *focus*(*i*); ratio between the number of *foci* and the number of contacts; age and sex of *focus*(*i*) and contact(s); clinical condition, period and regularity of treatment, rate of decrease of the bacteriological index, as well as existence of sporadic or recurrent reaction episodes of the *focus;* living conditions and size of the house; nutritional status and social, cultural, professional and religious habit of the individuals.

9. Dermatoglyphic studies

Dermatoglyphic studies on leprosy patients made with the aim of determining whether the dermal patterns of the palm and fingers might reveal some association with this disease (Enna, Elliott and Stockwell, 1970) are of doubtful validity. In fact, the use of dermatoglyphic analysis for diagnostic objectives show limitations even for congenital abnormalities due to chromosomal aberrations which, as it is well known, are usually associated to uncommon dermatoglyphic patterns.

We think that, for practical purposes, dermatoglyphic studies on leprosy should be directed first to the causes of the changes or destruction of dermopapillar patterns observed in different leprosy forms (Ribeiro, 1934, 1935), rather than to the search for questionable associations between leprosy and dermatoglyphics.

10. Studies on genetic polymorphisms and leprosy

Several genetic systems have been analysed in samples of leprosy patients of different populations with the hope of finding associations between this disease and some genetic polymorphisms. This search for possible pleiotropic effect of some common genes on the susceptibility to leprosy included the following genetic markers:

1. Taste sensitivity to phenylthiourea (Beiguelman, 1962_a, $1964_{a,b}$; Beiguelman and Marques, 1964).

2. ABO blood groups (Beiguelman, 1963, 1964_b; Hsuen, Thomas and Jesudian, 1963; Yankah, 1965; Verma and Dongre, 1965; Povey and Horton, 1966; Sehgal, Mathur and Rao, 1966; Prasad and Mohamed-Ali, 1966_a; Gupta and Gupta, 1966; Vogel and Chakravartti, 1966; Salzano, 1967; Salzano, Suñé and Ferlauto, 1967; Singh and Ojha, 1967; Saengudom and Flatz, 1967; Lechat *et al.*, 1967, 1968_a; Vogel, 1968; Vogel *et al.*, 1969, 1971, among others).

3. Secretion of ABH substances in the saliva (Sehgal and Dube, 1967).

4. Rh blood groups (Beiguelman, 1963; Yankah, 1965; Salzano, Suñé and Ferlauto, 1967; Lechat *et al.*, 1968_a).

5. Kell blood groups (Lechat *et al.*, 1968_a).

6. Kidd blood groups (Lechat *et al.*, 1968_a).

7. Duffy blood groups (Lechat *et al.*, 1968_a).

8. P blood groups (Lechat *et al.*, 1968_a).

9. Group specific component (Salzano and Hirschfeld, 1965; Lechat *et al.*, 1968_b).

10. Haptoglobins (Povey and Horton, 1966; Schwantes *et al.*, 1967; Lechat *et al.*, 1968_b).

11. Transferrins (Povey and Horton, 1966; Lechat *et al.*, 1968_b).

12. Beta-lipoprotein Ag^a (Lechat *et al.*, 1968_b).

13. Inv groups (Vogel *et al.*, 1971).

14. Glucose-6-phosphate dehydrogenase deficiency (Pettit and Chin, 1964; Beiguelman, Pinto Jr., Dall' Aglio, Da Silva and Vozza, 1966, 1968; Lechat *et al.*, 1968_b).

15. S Hemoglobin (Cézar *et al.*, 1971).

16. Beta-thalassaemia (Ramalho, Pinto Jr. and Magna, 1971).

17. HL-A antigens (Thorsby *et al.*, 1973; Dasgupta *et al.*, 1975).

Most of these investigations have been critically analyzed elsewhere (Beiguelman, 1967, 1972; Salzano, 1967; Vogel, 1968). They resulted negative or controversial, due probably to the fact that almost all genetic polymorphisms studied in relation to leprosy were chosen by hazard. Therefore, such studies are relevant for geneticists interested in verifying whether or not leprosy is one of the several forces that are maintaining the analysed polymorphic systems. However, in our opinion, they should not be encouraged among leprologists, because of not being considered as prioritary from the practical point of view.

At the present status of knowledge we think that the only polymorphic systems that may, perhaps, deserve the attention of these professionals are glucose-6-phosphate dehydrogenase (G-6PD), dapsone acetylator phenotype and NADH reductase. Nevertheless, such polymorphisms shall not be investigated with the aim of finding associations between them and leprosy, but with the main purpose of verifying the pharmacogenetic response to dapsone of G-6PD deficients, slow and rapid acetylators and heterozygous NADH reductase deficients. (For a review on these subjects see Beiguelman, 1976).

11. Chromosomal aberrations and leprosy

Beiguelman, Pisani and El-Guindy (1975) observed that dapsone is able to increase *in vitro* the frequency of aneuploidies (numerical chromosomal aberrations) and achromatic gaps (structural chromosomal aberrations), when added to leukocyte cultures of healthy individuals in a concentration of 4 μg/ml. This observation stimulated the investigation of the frequency of chromosomal aberrations in cultures of leukocytes of leprosy patients under dapsone therapy (Beiguelman and Pisani, 1976).

The chromosome analyses made on leukocyte metaphases of leprosy patients who were ingesting daily doses of 50 mg to 100 mg of dapsone has not shown any significant increase in aneuploil frequency. However, concerning the structural aberrations it was seen that leprosy patients presented a significant excess of cells with chromatid or chromosome breaks and gaps. At any rate, this excess could not be attributed to dapsone therapy because it was shown that the structural aberrations of chromosomes where not correlated to age, years of sulfone therapy or to concentration of dapsone in blood.

Though the higher frequency of such abnormalities may be supposed to be a consequence of leprosy itself, we can not exclude the possibility that conditions closely related to this disease are responsible for the increase of the observed structural aberrations. Moreover, it is too early to advance speculations on the meaning of this excess from the individual viewpoint, since we do not know whether most of the chromosomal and chromatid lesions observed are naturally repaired or not.

However, with respect to the genetic implications of these aberrations something may be advanced, in spite of not knowing whether the chromosomes of the germinative cells are affected or not in the same intensity as those of the leukocytes. Thus, if structural chromosomal abnormalities increased in the sperms and eggs of leprosy patients, a high proportion of spontaneous abortions would be

expected among couples including al least one leprous individual, since most of the zygotes with these abnormalities are unable to develop viable embryos. Nevertheless, it was pointed out previously that the frequency of spontaneous abortions among couples composed by lepromatous women married to healthy or lepromatous men was similar to that found in couples of the general population(Beiguelman, Marchi, Hama, Amin, Godoi and Baptista, 1965).

12. Conclusions

The literature on human genetics is shy of a methodology for investigating the genetic involvement of Man in the manifestation of infectious diseases. This is, obviously, the main reason why the foregoing sections have shown that research on genetics in leprosy has shed less light on this matter than it was desired, in spite of the great efforts devoted by several investigators.

Nevertheless, it is hoped that the experience accumulated by geneticists dedicated to leprosy since the last decade will help them to re-examine critically former investigations, and to outline other areas for further research, in the light of the recent and impressive advances in immunology and microbiology of leprosy.

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GENETICS IN LEPROSY

DAVID GLENN SMITH, BARUCH S. BLUMBERG, RICARDO S. GUINTO
AND FRED S. WITTENSTEIN

The search for genetic influences in leprosy predates the identification of Mycobacterium leprae (*M. leprae*) by Hansen (1875). Early theories of genetic involvement were based on the observation that the disease clustered in certain families (Danielssen and Boeck, 1848 ; Simpson, 1841). These theories were largely abandoned after Hansen's discovery. When it was recognized that etiologies involving pathogenic infections and genetic mechanisms were not mutually exclusive, interest in hereditary factors in susceptibility or resistance to leprosy was revived (see, for example, Aycock, 1940 ; 1941 ; 1948 ; Rotberg, 1957 ; Steiniger, 1941). Nevertheless, there have been few formal genetic studies of leprosy and genetic research in general has yielded contradictory results. We shall attempt to synthesize these results and include data from our own investigations. From this, inferences on the role of genetics in susceptibility to leprosy will be made.

EVIDENCE FOR GENETIC INFLUENCES

Epidemiologic research has provided some evidence for genetic influences upon susceptibility to leprosy. The following observations have consistently been made :

(1) While prolonged and intimate contact with lepromatous leprosy victims fails in most cases to result in transmission of infection, only casual contact often appears sufficient for transmission. Exposure alone, then, is insufficient to explain risk of infection. Indeed, it is extremely rare for all siblings of a sibship exposed to infection to develop leprosy (Spickett, 1962a).

(2) Risk of infection of contacts by open cases is related to their degree of kinship. The incidence of leprosy among sibs is higher when at least one parent has leprosy. Further, high inicidences of leprosy have been observed in some small highly inbred populations.

(3) Conjugal transmission of leprosy is rare (Mohamed Ali, 1965). Were non-genetic factors most important in transmission, spouses, who share similar environments, might be expected to infect each other more frequently.

(4) Different culturally assimilated racial or ethnic groups living in the same area maintain patterns of infection similar to those in their respective homelands (Spickett, 1962b).

(5) Risk of infection is not clearly related to age of exposure, family size, birth order, rural vs urban residence, diet, hygiene, climate, socio-economic factors or any other yet detectable environmental influences (Mohamed Ali, 1963 ; 1964 ; 1966 ; Badger, 1959 ; Doull, 1962).

The following evidence is also consistent with the operation of a genetic influence upon the clinical form which leprosy assumes :

(1) The immune response of lepromatous leprosy patients to *M. leprae* is defective, but is normal in patients with the tuberculoid form. One of these polar forms will not, in general, ever change to the other polar form.

(2) The proportions of leprosy cases which are of each polar form seem intrinsic to a population. Environmental changes are usually unable to alter these proportions in areas where the disease has long been endemic (Spickett, 1962b).

(3) Related contacts of lepromatous cases more often develop lepromatous as opposed to non-lepromatous leprosy than do unrelated contacts of lepromatous cases.

Genetic variability of *M. leprae* itself could contribute to the risk of infection or to determining the clinical form which develops. Its role, however, is considered to be relatively minor (Speckett, 1964). Multiple cases of infection within a family are usually assumed to originate from the same bacillary strain. The frequent occurrence of both polar forms within the same family, then, implies that the clinical form of the disease that develops is principally host rather than parasite-determined. Further, the hereditary characteristics of *M. leprae* which have been identified are not associated with the clinical course of leprosy in humans (Shepard and McRae, 1971). Nor does such phenotypic variability in *M. leprae* exhibit the geographical heterogeneity necessary to explain the geographic variations in patterns of infection which have been observed. Our review and analysis of new data will therefore be based on the assumption that the outcome of exposure to infection with *M. leprae* is entirely host-determined.

GENETIC APPROACHES TO THE STUDY OF LEPROSY

Three approaches have been taken in genetic studies of leprosy :

(1) The analysis of family data to select among alternative genetic hypotheses.

(2) Associations between phenotypic variants of polymorphic marker loci and leprosy.

(3) The comparison of concordance in the occurrence and form of leprosy in monozygous and dizygous twins. Each approach is reviewed separately in the following section.

Family Studies

Spickett (1962a) proposed an irregular dominant mode of transmission of susceptibility to leprosy. However, the pedigree data upon which this conclusion was drawn, said to include virtually all cases of leprosy in the study population, does not exclude an autosomal recessive mode of transmission. Further, his estimation of penetrance in the heterozygote by excluding the propositi was probably inappropriate since propositi do not introduce a bias when all cases of leprosy in a population have been ascertained. Prasad and Mohamed Ali (1966) have analyzed pedigree data which they conclude confirm the irregular dominant hypothesis. Their analysis employed estimates of expected phenotypic distributions in offspring which were made from expected frequencies of parental genotypic matings. These expected mating frequencies were calculated by assuming a frequency of 0.50 for the hypothesized susceptibility gene. No justification for this assumption was given, however. Given the relatively low prevalence of leprosy in all populations, a gene frequency of 0.50 would seem unrealistically high.

Beiguelman (1965) proposed an autosomal recessive hypothesis for transmission of susceptibility to lepromatous leprosy. He hypothesized that the failure to respond to the late lepromin (Mitsuda) test indicates a genetically determined inability to lyse (hence, the susceptibility to infection with) *M. leprae*. His analysis of segregation of the Mitsuda reaction, presented as evidence supporting this hypothesis, employed an estimate of the frequency of the hypothetical gene responsible for Mitsuda negative reactions. This estimate was the square root of the frequency of Mitsuda negative reactions and/or lepromatous leprosy in spouses of clinically ascertained leprous probands. The probability of ascertaining families in which both marriage partners have lepromatous leprosy (hence negative Mitsuda reactions) is greater than that of ascertaining families in which only a single partner has lepromatous leprosy (i.e., the proband). Thus, his gene frequency estimate is biased and probably inflated. As Mitsuda positive reactions are not always associated with resistance to leprosy (Guinto and Binford, 1965), the response is too complicated to equate with a given genotype (Beiguelman, 1967). It is now known that other bacterial antigens closely related to *M. laprae* are also able to inhibit the Mitsuda reaction (Kwapinski et al., 1975). Thus, Beiguelman's (1968 a ; b) argument that Mitsuda negativity indicates susceptibility of healthy individuals to *M. leprae* is not always valid. Finally, a significant difference between concordance of Mitsuda reactions in 38 monozygous and 89 dizygous twin pairs studies by Beiguelman (1971) was not found. Such a difference would be expected were the reactions significantly under genetic control.

The foregoing tests of simple genetic hypotheses were designed to compare the distribution of a trait (phenotype) within sibships with specific models for the segregation of genes presumed to determine this trait. The

binomial techniques employed by classical segregation analysis provide useful omnibus tests for rejecting simple genetic hypotheses. Such techniques, however, have little power to discriminate between patterns of allelic segregation expected under a genetic hypothesis and alternative causes of the distribution of a disease in sibships (Lilienfeld, 1959). As additional parameters, such as irregular dominance in heterozygote genotypes or variable penetrance, are added to modify genetic models they can become even more difficult to reject. The good fit of a set of data to genetic models, then, should be regarded as necessary but insufficient evidence on which to accept a genetic hypothesis.

MACTAN ISLAND, PHILIPPINES

In a study in endemic areas of India about 30 percent of the healthy individuals tested who were unaware of any contact with a case of leprosy exhibited cell mediated immunity to *M. leprae* (Godal, 1975). This immunity, indicated by lymphocyte transformation and leucocyte migration tests, suggests that there had been a previous or present subclinical infection with *M. leprae*. This implies that exposure sufficient to elicit a host response is extensive in endemic areas and is perhaps universal where most members of the population are in contact with a leprosy case. Given time for sufficient contact with, and incubation of, the parasite to occur, all individuals with the hypothesized susceptibility genotype should develop leprosy in such populations. Such a population, were it completely ascertained, would provide the ideal conditions for omnibus tests of genetic hypotheses.

We have analyzed data from a population, the municipality of Cordova on Mactan Island, near Cebu City, Philippines, which may fulfill these conditions. Over 99 percent of the population were examined. The methods of data collection, diagnosis and the epidemiology of leprosy in this population have been described extensively elsewhere (Doull, 1939 ; 1948 ; doull et al., 1945 ; Guinto et al., 1951 ; Rodriquez, 1975). Table 1 shows the proportion of sibships with leprosy-free parents exposed, since birth, to at least one close relative who had leprosy (Smith et al., 1977a). A close relative is here defined by a kinship coefficient of at least one-sixteenth. The sibships are subdivided into groups based on the date of marriage of their parents. Over 75 percent of those whose parents married after 1933, representing over three-quarters of all sibships studied, were so exposed. We can, then, assume that the probability of infection, given adequate time for exposure (i.e., age), is extremely high, and that most susceptible individuals develop leprosy after adequate time for incubation of the bacillus.

Table 2 shows the prevalence of lepromatous and non-lepromatous leprosy in offspring of matings of different types. Marked familial clustering of lepromatous, but not non-lepromatous, leprosy was observed. Lepromatous leprosy was about three times as prevalent when one parent had lepromatous leprosy than when neither parent had lepromatous ($x^2=36.6$, $p<0.0001$) or any form of leprosy ($x^2=35.9$, $p<0.0001$). For non-lepromatous leprosy, these differences were not seen.

The onset of leprosy, however, is a function of opportunity for contact with and incubation of *M. leprae* both of which are age-dependent. This opportunity, in a completely exposed population, can be regarded as the probability that an individual with the hypothesized susceptibility genotype has already developed leprosy. This probability may be interpreted as the penetrance, say k_x, of the genotype at exact age x. Table 3 presents the distribution of ages of onset, by five-year cohorts, of all males and females on Mactan Island who had developed lepromatous and all forms of leprosy by 1966. The values in the Y columns are the cummulative frequencies of all those with the disease at each age-of-onset group. They may be interpreted to mean, for example, that 74.6 percent of all females who ever develop lepromatous leprosy, do so before age 20. We have estimated the value of k, (defined above) for each single year of age by regressing the Y values upon the mid-points of the age-of-onset classes. The k_x value, then, is an estimate of the probability that an individual of exact age x at his most recent exam who has the susceptible genotype will have leprosy. A second order, rather than a linear, regression was employed to account for the more rapid increase in Y for earlier than for later age-of-onset classes.

The accuracy of the k_x estimates was tested by comparing the distribution of age-of-onset in this cross-sectional sample of the population with that of all individuals born prior to 1897 who ever developed leprosy during their lifetime. While k_x appeared to slightly overestimate penetrance for younger age groups,

in no case did the differences approach statistical significance. These penetrance values were then incorporated into segregation models appropriate for testing several simple genetic hypotheses for susceptibility to lepromatous and all forms of leprosy. The following genetic hypotheses were tested by our data which include 255 segregatable matings (i.e., those yielding at least one offspring with leprosy) :

(1) Susceptibility to lepromatous leprosy is transmitted as a recessive autosomal trait.

(2) Susceptibility to all forms of leprosy is transmitted as a recessive autosomal trait.

(3) Susceptibility to developing lepromatous leprosy, rather than non-lepromatous forms of leprosy, when infection *does* occur, is transmitted as an autosomal recessive trait.

(4) Susceptibility to developing lepromatous leprosy, rather than non-lepromatous forms of leprosy, when infection *does* occur, is transmitted as an autosomal dominant trait.

The last two of these hypotheses provide tests for fit of our data to simple genetic hypotheses for the regulation of the form of leprosy which develops in all sibs known to have been infected (i.e., who developed some form of leprosy). For these two analyses the size of a sibship was taken to be equal to the total number of sibs with some form of leprosy in that sibship. It is the sibs involved in the tests of these two hypotheses who are definitely known to have been sufficiently exposed to *M. leprae* to express the hypothesized phenotypic effect.

Our method of analysis employed a "complex segregation analysis." Such a method is required when variable penetrance can result in a bias in expected number of affected offspring and misclassification of the genotypes of mating phenotypes (Elandt-Johnson, 1970). The method and its application have been fully demonstrated elsewhere (Smith, 1977).

The segregation model used by this method is

$$\sum_{j=1}^{255} \sum_{i=1}^{n} \alpha_{ij} \, (rj^{s_j}) \, (\theta_i \, k_j)^{r_j} \, (1 - \theta_i \, k_j)^{s_j - r_j}$$

where the parameters are defined as follows :

s_j = numbers of sibs in the j^{th} sibship

r_j = numbers of leprous sibs in the j^{th} sibship

θ_i = *a priori* segregation ratio (i.e., θ=1/4 when both parents are assumed to be heterozygotes for the hypothesized susceptibility gene, 1/2 when one parent is heterozygous and the other homozygous for the gene and 1.00 when both parents are homozygous for the gene).

k_j = average of the penetrance values for the sibs in the j^{th} sibship

n = number of possible mating genotypes which the mating phenotype associated with the j^{th} sibship could represent

α_{ij} = probability that the mating phenotype associated with the j^{th} sibship is of the i^{th} possible mating genotype

The procedure for estimating α_i values for any sibship from a mating in which neither spouse had leprosy (i.e., an L- x L- mating phenotype) at the time of their last examination is illustrated in table 4 under the autosomal recessive hypothesis. The values are estimated in an analogous fashion for other hypotheses and mating phenotypes. This procedure requires the use of incidence of leprosy to estimate the frequency of the hypothetical gene in the population. The death of some who would have developed leprosy but died before doing so would bias gene frequency estimates downward. Further, there is evidence that beyond age 25 individuals with leprosy are subject to appreciably higher mortality than the healthy population. To avoid these sources of bias an estimate of incidence which more closely reflects the hypothesized underlying genotypes was made by dividing the life table incidence for those below 25 years of age (given by Doull, 1948) by the regression estimate of penetrance at age 25.

As indicated in table 5 none of the four hypotheses is supported by our data. Our analyses of a highly exposed population with a very high rate of ascertainment rejects a simple genetic hypothesis as the mechanism for transmission of susceptibility to the lepromatous or to all forms of leprosy.

Twin Studies

Monozygous (MZ) twins share all their genes in common while dizygous (DZ) twins

share, as do normal sibs, only half their genes in common. It is often argued that differences between rates of concordance for genetic traits in cotwins of these two twin types reflect only the difference in the proportion of genes in common. A greater concordance for the trait in MZ twins than in DZ twins, then, implies genetic causation while identical concordance rates for the two twin types implies non-genetic causation.

Although early studies of twins at least one of whom had leprosy have been described (Mantegazza, 1904 :; Ryrie, 1939 ; Brown and Stone, 1958 ; Keil, 1939), zygosity was either undetermined or not ascertained by rigorous and systematic observations. Other studies have reported only one or two sets of MZ twins (Ketkar et al., 1969 ; Doull, 1961) in whom similar clinical courses of the disease were observed. Spickett (1964) studied 29 pairs of Indian twins in which both cotwins had leprosy. All 14 MZ twins were concordant for form of leprosy while 4 of the 15 DZ twins were discordant in this regard. Mohamed Ali and Ramanujam (1964 ; 1966) carefully determined the zygosity of 35 twin pairs at least one of whom had leprosy. Concordance for leprosy among MZ twins was 82.6 percent (19 of 23 pairs) while that for DZ twins was only 16.7 percent (2 of 12 pairs). Only two of the 21 twin pairs concordant for leprosy (both MZ twins) were discordant for the form of leprosy.

The largest twin study of leprosy reported is that of Chakravartti and Vogel (1973) which compared 62 MZ and 40 DZ twins living in endemic areas of India. Concordance for leprosy between MZ and DZ cotwins was 59.7 and 20.0 percent, respectively.

The similarity of the environmental factors which might affect susceptibility may be somewhat greater for MZ than for DZ cotwins (Burt, 1966 ; Shields, 1962). This source of bias, however, is unlikely to be as serious (although in the same direction) as that introduced by the greater probability of ascertaining twins concordant than those discordant for leprosy (Cavalli-Sforza and Bodmer, 1971). For this reason, concordance rates for MZ twins may be somewhat inflated. Despite these sources of bias, however, the consistent finding of markedly higher concordance for leprosy for MZ than for DZ twins provides additional support for the operation of a genetic infiuence on susceptibility to leprosy.

Polymorphisms and Leprosy

The prevalence of leprosy in different phenotypes of numerous genetic markers whose pattern of segregation is known has been studied principally during the last decade. Such studies represent an attempt to identify polymorphisms or closely linked loci which they mark whose gene products affect susceptibility to leprosy.

RED CELL ANTIGENS

Polysaccharide antigens similar to the *A*, *B* and *H* red blood cell antigens occur in some parasites. Sharing antigenicity with a parasite might immunologically affect the host's antibody response to infection with that parasite (Otten, 1967). Such a mechanism has been proposed for associations between several diseases and *ABO* phenotypes (Clarke, 1961 ; Helmbold and Vogel, 1962).

Some studies in India have shown blood type *O* to be more common among leprosy patients than among healthy controls (Ghosh and Mukherjee, 1970a ; b ; Vogel et al., 1971a). Other studies of Indian (Chakravartti and Vogel, 1973), Siamese (Saengudom and Flatz, 1967) and West African (Languillon et al., 1971a) samples have reported type *A* to be more frequent among leprosy (usually lepromatous) patients. The severity of eye involvement in lepromatous leprosy in Thailand appeared to be greater for patients with *A* or *AB* than for those with *B* and *O* ($p < 0.05$) (Vogel et al., 1969). But since this was the only statistically significant association between *ABO* phenotypes and leprosy in a total of 36 tests, it may well have been spurious. This association was not found in a sample of Indian patients with lepromatous leprosy (Vogel et al., 1971a).

Other Indian (Ketkar, 1970 ; Vogel and Chakravartti, 1966 ; Vogel et al., 1971b) and West African (Faye et al., 1971 ; Languillon et al., 1973) studies have found no associations between *ABO* phenotypes and leprosy. Combining data from forty-one studies Vogel (1968 ; Vogel et al., 1969 ; 1971a) found a slight, but insignificant, deficiency of type *O* in patients with lepromatous leprosy compared with those with non-lepromatous forms of leprosy. The x^2 for heterogeneity among these various population data, however, was highly statistically significant. Thus, it is inappropriate to regard them as a homogeneous sample for analysis. Better methods for combining samples from different popu-

lations for this purpose are available (Woolf, 1955).

Vogel et al. (1971a) identified an apparent interaction between the *A* red blood cell type and the *Inv* (1) gammaglobulin phenotype in one of two populations which were studied. The two-locus phenotype occurred significantly more frequently than expected in lepromatous but not in non-lepromatous leprosy patients in a population from Thailand. This association, however, was not confirmed in a set of Indian data.

Lessa (1954) reported that *Rh* negative individuals are more common among leprosy patients than in the general population, but this has not been observed in other studies (Faye et al., 1971 ; Languillon et al., 1971a ; 1973). No red cell antigen has consistently been found to be associated with any form of leprosy.

HISTOCOMPATIBILITY (HLA) ANTIGENS

The histocompatibility antigens determine, or mark regions which determine, cell mediated immune responses and are associated with liability to a number of diseases related to immune status (McDevitt and Bodmer, 1972 ; Ryder et al., 1974 ; Ritzmann, 1976). Differences in cell mediated immune responses clearly distinguish the lepromatous from all other forms of leprosy and from the non-infected (or subclinically infected) state. Consequently, *HLA* phenotypes and haplotypes are prime suspects for host factors influencing the outcome of infection with *M. leprae*.

Different population samples of lepromatous leprosy patients have shown a preponderance of *HLA-B*8 (Dasgupta et al., 1975), *A*10 (Smith et al., 1975) and *B*14 (Kreisler et al., 1974). *HLA-A*5 occurred statistically significantly more frequently (Smith et al., 1975) and *HLA-A*9 less frequently (Dasgupta et al., 1975) in tuberculoid leprosy patients than in lepromatous leprosy patients. None of these associations are statistically significant, however, when p values are corrected for the number of antigens tested ($p'=p$ x the number of antigens tested, Miller, 1966). In a mixed Mexican-Mestizo sample of 50 leprosy patients from Mexico City statistically significant deficiencies of *HLA-A2* and *A3* (Escobar-Gutierrez et al., 1973) were found. Difficulties were encountered in culturing the lymphocytes and typing for *HLA* specificities, however. Further, both lepromatous and non-lepromatous patients were combined for the analysis. It is therefore difficult to assess the meaning of these results. *HLA-Bw*21 was found in one study (Thorsley et al., 1973) to occur more frequently among 19 lepromatous and 20 non-lepromatous leprosy patients than among healthy controls. The small sample sizes and the similar outcome for both forms of leprosy, upon whose clinical differences the comparisons of *HLA* phenotypes is usually justified, suggest that this association could be fortuitous.

The extreme complexity of the *HLA* region, cross cultural variability in frequencies of the many specificities, variation in sampling procedures and small size of samples reported prevent any useful comparisons of studies in different populations. Such comparisons will require large samples obtained from many different populations, a time consuming and costly operation. Only large samples can reveal associations between forms of leprosy and haplotypes, which are more likely than single locus phenotypes to mark adjacent regions of the chromosome. The statistical significance of these and other associations must be evaluated in light of the (usually) large number of antigens studied.

RED CELL PROTEINS

Phenotypic variation in two red cell proteins, hemoglobin (*Hb*) (*A*llison, 1954) and glucose-6-phosphate-dehydrogenase (G-6-P-D) (Luzzatto et al., 1969) are known to affect susceptibility to malaria. The geographical distribution of the abnormal hemoglobin Hb^s is similar to that of leprosy in Africa and Asia. However, no association was found between Hb^s and any form of leprosy in large samples of Negro and Caucasian patients from Africa (Cezar et al., 1974 ; Languillon et al., 1971a ; 1973). In two studies the phenotype associated with G-6-P-D deficiency was found in higher frequencies among leprosy patients in India (Kher and Grover, 1969 ; Benait and Junnarker, 1971). The proportion of leprosy patients (most of whom in both studies had the lepromatous form of the disease) who were G-6-P-D deficient was about the same in both studies. This and the large number of both populations sampled provide some assurance that sampling errors are not responsible for the significant association. Large studies of African (Languillon et al., 1972), Philippine

(Lechat et al., 1968) and Brazilian (Beiguelman et al., 1968) populations, however, failed to confirm the association. Benait and Junnarker (1971) found all lepromatous leprosy patients with acid fast baccilli in their bone marrow to be G-6-P-D deficient. Variations among the populations in these and other clinical features of the disease could be responsible for the contradictory findings and should be further investigated.

PHENYLTHIOCARBAMIDE (PTC)

Individuals homozygous for the recessively inherited inability to taste PTC are significantly more susceptible to nodular goiter (Boyce et al., 1976). However, no *a priori* expectations of a similar increased susceptibility to any infectious disease suggests itself. No such association has, indeed, been found (Beiguelman, 1964) between leprosy and PTC taste sensitivity.

SERUM PROTEIN POLYMORPHISMS

Lepromatous leprosy patients, compared with both healthy controls and non-lepromatous leprosy patients, more often exhibit persistent infection with Australia antigen (*HbsAg*) in India (Ananthakrishanan et al., 1972 ; Blumberg and Melartin, 1970 ; Dutta and Saha, 1973 ; Joshi et al., 1974 ; Kelkar et al., 1974), Greece (Papaevangelou et al., 1972), Mexico (de las Aguas and del Hierro, 1971), Africa (Francis and Smith, 1972 ; Languillon et al., 1971b ; 1973) and the Philippines (Blumberg and Melartin, 1970 ; Blumberg et al., 1967 ; 1970). As only outpatients or inpatients (but not both) were used in some studies, a greater opportunity for infection of lepromatous than of non-lepromatous patients with *HbsAg* due to more frequent institutionalization of lepromatous cases would appear unlikely. In other studies from India (Bedi et al., 1975 ; Kelkar et al., 1973), Brazil (Salzano and Blumberg, 1970), Greece (Papageorgion et al., 1972) and Africa (Lechat et al., 1973 ; Ananthakrishnan et al., 1972 ; Swanepoel and Cruickshank, 1972), however, this association was not found.

Of all the associations studied that between *HbsAg* and lepromatous leprosy is the most commonly found. Of the seven studies which failed to identify such an association small sample sizes used in two may have led to errors in sampling (Bedi et al., 1975 ; Papageorgion et al., 1972). The Brazilian study (Salzano and Blumberg, 1970) is consistent with the observation that significant associations are not generally found where *HbsAg* occurs in very low frequencies. In another study frequencies of *HbsAg* were higher in patients with lepromatous leprosy than either those with tuberculoid leprosy or normal controls, but these differences were not statistically significant (Ananthakrishnan et al., 1972). Swanepoel and Cruickshank's study (1972) was conducted in Rhodesia where frequencies of *HbsAg* vary considerably from region to region. Since their study included samples of controls and leprosy patients from different geographical areas, the controls may not have provided a valid comparison. Most studies which have employed large samples of leprosy patients and randomly selected controls from populations in which *HbsAg* occurs in high frequencies have confirmed the association between *HbsAg* and lepromatous (but not non-lepromatous) leprosy. A common impairment of cell mediated immunity in infections with both *M. leprae* and *HbsAg* might explain the association.

Haptoglobins bind and probably help dispose of hemoglobin molecules freed during cell destruction. As the haptoglobin phenotype Hp (1-1) has greater binding capacity than other phenotypes, a selective force affecting this phenotype might occur in tropical areas where anemic and other hemolytic conditions are common. The prevalence of leprosy is also greatest in tropical areas. As the Hp^1 gene appears to increase in frequency nearer to these areas (Buettner-Janusch, 1966), an association between the Hp^2 gene and leprosy would provide a balancing selective force for maintaining the *Hp* polymorphism. Most studies, however, have revealed no relationship between *Hp* phenotypes and any form of leprosy (Walter et al., 1970; 1972; Schwanter et al., 1967). An excess of the Hp (1-1) phenotype among lepromatous leprosy patients, as opposed to tuberculoid patients and controls, was found in a Philippine population by Lechat et al. (1968). Hp (1-1) was found in excess among lepromatous leprosy patients compared with controls and with tuberculoid leprosy patients in Angola, Africa (Ananthakrishnan et al, 1973). In this study tuberculoid leprosy patients had significantly lower frequencies of Hp^{2-2} than did normal controls. These outcomes, however, could be spurious. First, three of the four significant tests ($p<0.05$) performed in this last marker study are expected as type I errors given the large number (53) of tests performed. Second, as all possible

multiple pairwise comparisons among disease classes were made, all of the tests are not independent contrasts (Bancroft, 1968:100). Thus, the number of type I errors expected for the analysis at the 0.05 level of probability may actually be *greater* than 3.

The group specific protein gene Gc^1 seems to occur in lower frequencies in areas where the prevalence of leprosy is highest (Buettner-Janusch, 1966). Although this polymorphism is not known to be related to any disease, an excess of the Gc^1 gene among individuals with lepromatous leprosy could explain this distributional pattern since the lepromatous form of the disease decreases fertility (Beiguelman et al., 1965; Smith et al., 1977b). The Gc^{1-1} phenotype has been found in higher frequencies in all leprosy patients than in healthy controls (Goedde et al., 1975; Spielmann et al., 1970; Walter et al., 1972). Another study found these same differences but they were not statistically significant (Salzano and Hirschfeld, 1965). Further studies are needed before generalizations can be made.

Low levels of serum cholinesterase, a condition known to result from homozygosity for an atypical autosomal gene, E_1^a, have been reported in patients who recover abnormally slowly from paralysis induced by the muscle relaxant Scoline. It has been observed that some leprosy patients administered Scoline exhibit similar behavior (Thomas and Job, 1972). Their pseudocholinesterase levels, however, were not tested. A study in South India found that dibucaine was significantly less able to inhibit serum cholinesterase (i.e., thus yielding a low dibucaine number) in lepromatous than in both tuberculoid leprosy patients and normal controls from India (Thomas and Job, 1972). A low dibucaine number is sometimes associated with the presence of the atypical serum cholinesterase gene. However, this association was not found in a sample of Ethiopian leprosy patients (Agarwal et al., 1973).

Transferrins, which migrate in the β-globulin fractions of serum, bind with and transport iron to and from bone marrow and other tissues where they form an important constituent of hemoglobin and various enzymes. The polymorphic variants of transferrins are controlled by genes segregating at a locus which appears to be linked with the locus controlling pseudocholinesterase levels (Renwick, 1969). These variants have differential iron binding capacities. Although no evidence is available, it has been suggested that transferrin-iron complex inhibits the multiplication of viruses in the body (Buettner-Janusch, 1966) explaining the decrease in transferrin levels during episodes of infection (White et al., 1959). Several populations have been studied to detect associations between transferrin phenotypes and the polar forms of leprosy (Ananthakrishnan et al., 1973; Goedde et al., 1975; Lechat et al., 1968; Walter et al., 1970; 1972); none has been found.

Two codominant alleles control the synthesis of the third component of complement, C3. C3 enhances the binding of antigen-antibody complexes to leukocytes and the phagocytosis of antibody-coated microorganisms by leucocytes and macrophages (Jawetz et al., 1976). A silent (but rare) allele has also been identified for which there is no detectable gene product. Homozygosity for this gene has been shown to be associated with higher susceptibility to some bacterial infections (Alper et al., 1972). The level of C3 in human serum has also proved useful in the diagnosis and prognosis of several diseases (Schurr and Austen, 1968). Levels of C3 in leprosy patients, relative to control subjects, have been found to be higher in some studies (Agarwal et al., 1974) but lower in others (Shwe, 1972; Shwe and Petty, 1972). The frequencies of the C3 phenotypic variants of the two common alleles in leprosy patients do not appear to differ from those in normal controls (Ananthakrishnan et al., 1973; Agarwal et al., 1974). Neither do these variants differ in total C3 concentration (Agarwal et al., 1974; Srivastava et al., 1975a; b). Further, the immune activities associated with C3 appear to be normal in those with lepromatous leprosy (Sheagren, 1969). A significant difference in C3 concentration between patients with leprosy and healthy controls is more likely due to the clinical course of the disease itself rather than to a causal factor in the disease.

The polymorphism controlling the synthesis of α_1-antitrypsin, a serum glycoprotein, is controlled by several codominant genes. Two of the less common of these genes, Pi^s and Pi^z, are associated with low concentrations of α_1-antitrypsin and with certain pulmonary diseases as well (Keuppers, 1971). Eriksson (1965) has proposed that individuals carrying these atypical genes have a greater susceptibility to tissue damage by proteolytic enzymes

of granulocytes and macrophages which are not sufficiently inactivated. If so, a similar process might influence the clinical course of leprosy in susceptible individuals. One study of an African population has proved consistent with this hypothesis, the less common phenotypes occurring in significantly higher frequencies among lepromatous leprosy patients (Ananthakrishnan et al., 1973). Other studies of an African and an Indian population found the same relationship but the differences were not statistically significant (Walter et al., 1970; 1972). One of these studies (Walter et al., 1972) found the atypical *Pi* phenotypes to be statistically significantly associated with three features of the disease in patients with lepromatous leprosy: the absence of paralysis and reactivity and the presence of nodular, as opposed to macular, skin lesions. A larger sample for the tests might have revealed other significant relationships.

It has been suggested that phenotypic variants in *Inv* and *Gm,* polymorphisms of the gamma globulin fraction of human serum, might differ in the amount of gamma globulin formed hence in the intensity of immune responsiveness. No difference has been found, however, between the phenotypic distributions of *Inv* of controls and patients with any form of leprosy (Ananthakrishnan et al., 1973; Vogel et al., 1971b). Further, *Inv* phenotypes do not appear to differ in total amount of serum gamma globulin (Vogel et al., 1971b), nor do lepromatous leprosy patients have lower levels of immunoglobulins than controls (Sheagren, 1969). The distribution of *Gm* phenotypes of controls and those of patients with all forms of leprosy were found to be homogeneous in a study of an African population (Ananthakrishnan et al., 1973).

Additional serum protein polymorphisms which have been studied are ceruloplasmin (*Cp*) and B_2-glycoprotein I (*Bg*). Walter et al. found both homozygote *Bg* genotypes to be more common among leprosy patients in Mozambique (1970) yet less common among leprous males (but not females) in West Bengal, India (1972). Only for the Indian population was the distribution of the form of leprosy known. Here, female patients with lepromatous leprosy were less frequently, but not significantly so, of the heterozygote phenotype. In Mozambique the Cp^B phenotype was found to be statistically significantly more common among leprosy patients than among controls. All other phenotypes were rare among patients (Walter et al., 1970). In India no such relationship was found (Walter et al., 1972).

Using other markers such as the Lewis blood group system and the phosphoglucomutase loci phenotypic heterogeneity between patients with leprosy and normal controls has been reported (Spielman et al., 1970), but confirming studies have not, to our knowledge, been conducted.

Yasuda and Morton (1967) have shown that inter-village kinship coefficients for common genetic markers decrease with distance and can be fit by a monotonically decreasing function. This function is analogous to an intraclass correlation coefficient between gene frequencies of villages separated by identical distances. Bechelli et al. (1973) attempted to compare such a function with correlations between prevalence rates of village pairs separated by different geographic distances but were unsuccessful. Differences in village prevalence rates, however, could be regarded as functions of inter-village genetic distances only if all 118 villages studied were equally exposed to infection. A similar study which, for example, could demonstrate similar rates of "subclinical" infection might ensure more homogeneous opportunity for infection among a set of villages and prove more informative.

Most of the significant associations identified by the marker phenotype analyses reviewed here have involved only the lepromatous form of leprosy. Yet no marker phenotype studied has shown a consistent association with this or any other form of leprosy. It is still too early to judge the meaning of these contradictory results from different population studies. Phenotypic variation between controls and patients with (especially lepromatous) leprosy which was reviewed here follows a more consistent pattern for the *Gc* and *Pi* markers and also for the *HBsAg* antigen which has some characteristics of a polymorphism. Further studies of the association of these markers with various aspects of the lepromatous form of leprosy which exhibit clinical and immunological variation could enlighten the meaning of these apparent relationships between genetic variation and resistance to leprosy. In general, marker studies conducted heretofore provide little such enlightenment.

Few of these studies have sought associations which are derived from explicit *a priori*

functional expectations that the polymorphism is linked to hypothetical genes responsible for resistance to infection with *M. leprae* or directly alters resistance (Ananthakrishnan et al., 1973). In some cases the large sampling errors of the small sample sizes used in these studies may have led to statistically significant associations which are spurious. In other cases the few significant associations found at the 0.05 level of probability could be expected given the large number of statistical tests performed. Some studies have treated the polar or other forms of leprosy separately while others have not distinguished between different forms of leprosy in these tests. This has led to ambiguities in comparing the outcomes of independent tests of association from different populations. A standard and highly efficient statistic for such tests has been suggested by Woolf (1955) but it was not always employed in the studies reviewed here. This statistic is not influenced by variation in either the disease incidence or phenotype frequencies and thus allows the combining of weighted estimates obtained from many different populations. Attempts should also be made to detect effects of interactions between different loci upon susceptibility to lepromatous leprosy. Finally, even consistent and strong associations between polymorphisms and diseases may allow that the genes involved play only a negligible role in susceptibility to the disease relative to the role of the environment or of many other genes (Edwards, 1965). The large variety of polymorphisms found to be associated with lepromatous leprosy in different populations suggests that if there is a genetic influence a large number of independent genes may affect susceptibility to that disease.

The Multifactorial Hypothesis

Brown (1956; 1959) has argued that many genes might be responsible for susceptibility to leprosy. Spickett (1964) has argued that a multifactorial (polygenic) hypothesis would require viewing leprosy as a continuously distributed characteristic. This, at that time, did not seem likely. Recent studies, however, indicate that competence of the cell mediated immune response to *M. leprae,* measured by leucocyte migration inhibition and lymphocyte transformation, may be continuously distributed in human populations. Such a distribution coincides roughly with the scale of severity of infection from the highly resistant polar tuberculoid form to the non-resistant polar lepromatous form of leprosy (Myrvang, 1975). Similar tests also revealed evidence of sub-clinical infection with *M. leprae* in a large proportion of healthy contacts of leprosy patients (Godal and Negassi, 1973) and in a substantial proportion of healthy members of endemic populations who were unaware of any contact with leprosy victims (Godal, 1975). The polar lepromatous form could, then, represent the threshold of a continuum of resistance above which occurs a complete lack of resistance. This continuum might begin with asymptomatic sub-clinical infection and progress through the non-lepromatous range reflecting decreasing levels of resistance. At some point beyond the non-lepromatous range immune responses become totally inadequate. Many genes which affect the immunological defense system might determine one's position on this scale after exposure to *M. leprae.* Some of these genes might be identical to, interact with or be marked in the genome by some of the polymorphisms found in some populations to be associated with lepromatous leprosy.

Mactan Island, Philippines

If resistance to infection could be quantitated for an entire population in which leprosy is endemic, the hypothesis that resistance, hence susceptibility to leprosy, is transmitted as a multifactorial trait could be tested by the standard regression techniques of quantitative genetics (Falconer, 1960). As only the form of leprosy is usually known for such populations, the level of resistance is known only for victims of lepromatous leprosy. The complete lack of resistance exhibited by these victims is analogous to a multifactorial threshold trait. The standard regressions of phenotypic values of probands upon those of their relatives, employed in quantitative genetics to estimate the degree of genetic determination, are not possible because only the presence or absence of such a trait can be detected. Falconer (1965), however, has developed a method by which to estimate the degree of genetic determination for multifactorial threshold traits. By regarding lepromatous leprosy as a threshold characteristic we can estimate its heritability (h^2). If resistance to infection *is* continuously distributed this should provide an estimate of h^2 for leprosy in general. Other forms of leprosy, associated with varying levels of resistance cannot be regarded as a threshold trait and should yield a much lower estimate of h^2 when analyzed in this fashion.

We have estimated heritability for susceptibility to lepromatous and to all forms of leprosy on Mactan Island. Following the method of Falconer (1965) we have employed estimates of coefficients of regressions of liabilities of relatives of propositi to the disease upon liabilities of propositi to the disease to estimate h^2. This method assumes that expression of the threshold characteristic results from the additive effects of many codominant genes in the absence of epistasis or gene-environment interactions. A heritability of 100 indicates total genetic determination of (i.e., no environmental contribution to) susceptibility. Heritability estimates near zero are indicative of non-genetic determination. Estimates well below zero or above 100 can be regarded as clear rejections of the multifactorial hypothesis and low h^2 estimates imply that if genes do affect susceptibility, their contribution is minimal.

For our analysis the first degree relative sib-sib pairs and parent-sib pairs were combined to provide the largest possible samples with the least sampling error for the estimate of the regression coefficients (b). Then $h^2 = b/r$ where r is the kinship coefficient (1/2 in this case) relating relatives to propositi. Since the prevalence of leprosy differs in males and females an independent estimate of h^2 was made for each sex. For this purpose only like-sexed relative pairs (i.e., male-male and female-female) could be used since the genetic component of liability to a multifactorial threshold characteristic need not depend upon the same genes in the two sexes (Falconer, 1965).

Our results are given in table 6. When lepromatous leprosy is regarded as a threshold trait the estimate of heritability in males, 71.7 ± 6.8, is higher than that in females, 53.0 ± 14.0. While such a difference could result from different variances in liability derived from environmental causes for the two sexes, the two estimates do not differ within the range of their standard errors. Since the two h^2 estimates do not differ an average value can be estimated by weighting the regression coefficients of each by the inverse of their sampling variances. The variance of this average estimate is the inverse of the summed weights. As shown in table 6 the average h^2 is 68.1 ± 6.1. When, on the other hand, "all forms of leprosy" is regarded as the threshold trait the two estimates of h^2 are much lower and *do* differ within the ranges of their standard errors.

The outcome of our analysis suggests that over two-thirds of resistance to infection with *M. leprae* would be determined by genes were the multifactorial hypothesis valid. If some of these genes exhibit dominance, however, this estimate may be slightly inflated. This estimate is similar in magnitude to heritability estimates for other diseases suspected to be inherited as multifactorial characteristics such as harelip, rheumatic fever and diabetes mellitus (Cavalli-Sforza and Bodmer, 1971). While the outcome of the preceding analysis does not warrant acceptance of the multifactorial hypothesis, it is certainly consistent with this hypothesis.

Conclusions

Epidemiologic and family studies, genetic marker analyses and twin studies all suggest a strong genetic contribution to susceptibility to developing leprosy when infected with *M. leprae*. While inconsistent with a principal gene effect, the evidence supports the multifactorial determination of the adequacy of the host's cell mediated immune response to resist infection with *M. leprae*. Further genetic marker studies offer an encouraging prospect for identifying both susceptible individuals and the genetic mechanisms involved in susceptibility. Larger and longitudinally designed twin studies which are free of ascertainment bias could provide further valuable information on the mode of inheritance of susceptibility as would the comparisons of estimates of heritability for a variety of relative-pairs (i.e., sib-sib, parent-child, cousin-cousin, uncle-nephew, grandfather-grandchild, etc.) in the same population. It is hoped that these goals will attract a greater interest among human geneticists.

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TABLE 1

COMPARISON OF OBSERVED AND EXPECTED NUMBERS OF SIBSHIPS EXPOSED AT TIME OF PARENTS MARRIAGE TO A CASE OF LEPROSY IN A MATERNAL OR PATERNAL RELATIVE[1]

	Observed			Expected			
	Exposed	Un-exposed	%	Exposed	Un-exposed	%	$X^2(1)$
-1914	38	146	20.7	37.0	147.0	20.1	0.00
1915-1932	125	67	65.1	112.8	79.2	58.8	1.39
1933-1940	107	34	75.9	91.4	49.6	64.8	3.62
1941-1948	125	21	85.6	106.0	40.0	72.6	6.71*
1949+	355	13	96.5	291.2	76.8	79.1	50.00**
Total	750	281	72.8	662.7	368.3	64.3	31.83**

[1]-X^2 (1) value is corrected for continuity with Yate's correction factor.
* and ** = significance at the 0.01 and, at least, the 0.0001 level of probability.

TABLE 2

DISTRIBUTION OF LEPROMATOUS (L) AND NON-LEPROMATOUS (NL) LEPROSY IN OFFSPRING BY DISEASE TYPE OF PARENTS[1]

	No. Families	Total No. Offspring	No. L+	%L+	No. NL+	%NO+
(L—)×(L—)	1156	6906	143	0.0207	177	0.0256
(L+)×(L—)	64	323	24	0.0743	9	0.0279
(L—, NL—)×(L—, NL—)	1027	6167	129	0.0209	169	0.0274
(NL+)×(L—, NL—)	131	745	15	0.0201	8	0.0107

[1](L+) and (L—) refer, respectively, to parents with and without lepromatous leprosy, and (NL+) and (L—, NL—) refer, respectively, to parents with non-lepromatous leprosy and with neither form of leporsy. The prevalence of lepromatous and non-lepromatous leprosy in the general population is, respectively, 0.023 and 0.027.

TABLE 3

DISTRIBUTION OF LEPROMATOUS AND ALL FORMS OF LEPROSY AND ESTIMATES OF PENETRANCE FOR MALES AND FEMALES BY AGE GROUP OF ONSET[1]

	Males				Females			
Age of Onset	Lepro-matous Leprosy	Y	All forms of Leprosy	Y	Lepro-matous Leprosy	Y	All forms of Leprosy	Y
0-4	0	.000	4	.014	0	.000	3	.020
5-9	16	.098	37	.139	10	.170	34	.247
10-14	51	.409	83	.419	13	.390	35	.480
15-19	38	.640	60	.622	21	.746	33	.700
20-24	21	.768	39	.753	8	.881	18	.820
25-29	14	.854	22	.828	1	.898	3	.840
30-34	6	.890	13	.872	2	.932	7	.887
35-39	9	.945	13	.916	2	.966	5	.920
40-44	3	.963	8	.943	0	.966	4	.947
45-49	1	.970	2	.949	0	.966	1	.953
50-54	1	.976	2	.956	2	1.000	7	1.000
55-59	2	.988	8	.983	0		0	
60-64	1	.994	2	.990	0		0	
65-69	0	.994	0	.990	0		0	
70-74	1	1.000	3	1.000	0		0	
75-79	0		0		0		1	
	164		296		59		151	

[1]To avoid overestimating Y at higher ages, female penetrance was considered to be maximal by age 55 despite the single female whose age of onset for a non-lepromatous form of leprosy was above age 75.

TABLE 4

METHOD FOR ESTIMATING α_i FOR AN L— × L— PHENOTYPE MATING: AUTOSOMAL RECESSIVE HYPOTHESIS

Possible Genotypic Mating[1] Father		Mother	i	θ_i	Expected Mating Frequency[2]		α_i
L^1/L^0	×	L^1/L^0	1	$\frac{1}{4}$	$2p_{♂} q_{♂} \times 2p_{♀} q_{♀}$	= A	A/X
L^1/L^1 (NE)	×	L^1/L^0	2	$\frac{1}{2}$	$q^2_{♂} (1-k_{♂}) \times 2p_{♀} q_{♀}$	= B	B/X
L^1/L^0	×	L^1/L^1 (NE)	3	$\frac{1}{2}$	$2p_{♂} q_{♂} \times q^2_{♀} (1-k_{♀})$	= C	C/X
$L^1(L^1$ (NE)	×	L^1/L^1 (NE)	4	$\frac{1}{1}$	$q^2_{♂} (1-k_{♂}) \times q^2_{♀} (1-k_{♀})$	= D	D/X
					Total	= X	

[1] L^1 represents the recessive gene whose homozygote state confers susceptibility to leprosy when infected and L^0 its allele. NE indicates a homozygous recessive state in which leprosy is not expressed in the phenotype due to incomplete penetrance of the genotype.

The frequency of the hypothetical gene L^1 in males and females in the general population, $q_{♂}$ and $q_{♀}$ respectively, was estimated as $\sqrt{f'}$ and $1 - \sqrt{1 - f'}$ for the autosomal recessive and dominant hypotheses, respectively, where f' is the life table incidence of leprosy below age 25 (1933-1941) divided by the penetrance value of the L^1/L^1 genotype at age 25. $f'_{♂}$ and $f'_{♀}$ are .034 and .014 respectively for lepromatous leprosy and .061 and .037 respectively for all forms of leprosy combined. k is equal to the penetrance value for a parent of that sex at his (hers) age when last examined for the presence of leprosy.

TABLE 5

SEGREGATION ANALYSIS OF SUSCEPTIBILITY TO LEPROSY [1, 2, 3]

Analysis	Neither Parent with Leprosy				One Parent with Leprosy				Both Parents with Leprosy				Total			
	N	E(r)	T	X^2	N	E(r)	T	X^2	N	E(r)	T	X^2	N	E(r)	T	X^2
A♂		82.04	87	0.92		15.56	16	0.04		2.19	0	5.67*		99.79	103	0.31
A♀		73.87	48	27.65****		12.79	9	3.65		.60	0	1.56		87.26	57	32.25****
A_T	106	155.90	135	8.55**	19	28.35	25	1.26	3	2.79	0	7.24**	128	187.04	160	11.99***
B♂		171.32	190	6.02*		20.56	21	0.03		4.05	1	5.18*		195.93	212	8.87*
B♀		154.26	98	60.62****		16.90	12	4.28*		1.53	0	3.47		171.16	110	67.19****
B_T	218	325.59	288	12.82***	24	37.46	33	1.58	5	5.58	1	8.48**	247	368.63	322	17.36****
C													37	57.72	72	25.90****
D													37	65.70	72	4.33*

[1]A = lepromatous leprosy assuming variable penetrance
B = all forms of leprosy assuming variable penetrance
C = lepromatous leprosy in infected sibs—recessive autosomal hypothesis
D = lepromatous leprosy in infected sibs—autosomal dominant hypothesis

[2]*, **, *** and **** = significant to at least the 0.05, 0.01, 0.001 and 0.0001 levels of probability, respectively.

[3]N is the number of sibships, E(r) is the number of sibs with leprosy expected under the genetic hypothesis and T is the number of sibs with leprosy actually obsesred. $X^2=(E(r)-T)^2/V(r)$ with one degree of freedom where V(r) is the expected variance in the number of offspring with leprosy (see Smith, 1977).

TABLE 6

ESTIMATE OF HERITABILITY (h^2) OF LEPROMATOUS AND ALL FORMS OF LEPROSY FOR MALES AND FEMALES BASED ON THE MULTIFACTORIAL THRESHOLD HYPOTHESIS FOR SUSCEPTIBILITY[1]

Lepromatous Leprosy

Propositi	Sib	Number cases of leprosy in sibs of propositi	Prevalence of leprosy in sibs	Mean liability: Relatives of propositi	Mean liability: General Population	Estimate of heritability: h^2	± S.E.
Male	Male	62	.1442	1.062	1.872	71.7	6.8
Female	Female	8	.0661	1.505	2.175	53.0	14.0
Weighted	Average					68.1	6.1

All Forms of Leprosy

Propositi	Sib	Number cases of leprosy in sibs of propositi	Prevalence of leprosy in sibs	Mean liability: Relatives of propositi	Mean liability: General Population	Estimate of heritability: h^2	± S.E.
Male	Male	133	.1334	1.110	1.552	44.6	5.3
Female	Female	36	.0673	1.497	1.792	27.0	7.8
Weighted	Average					39.0	4.4

[1]For h^2 estimates the general population prevalences of lepromatous leprosy of .0306 and .0148 (115 and 49 cases) for males and females respectively were used, and for all forms of leprosy, the prevalences .0603 and .0366 (226 and 122 cases) for males and females respectively were used.

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INDIGENOUS LEPROSY IN THE NINE-BANDED ARMADILLO

WAYNE M. MEYERS, CHAPMAN H. BINFORD, GERALD P. WALSH

In the general article on leprosy, we mentioned the lepromatous leprosy infection that follows inoculation of *Mycobacterium leprae* into the nine-banded armadillo (*Dasypus novemcinctus*). Dr. Eleanor E. Storrs, at the Gulf South Research Institute (GSRI), New Iberia, Louisiana, first used the armadillo for leprosy research in 1971. In 1975, the staff of GSRI reported the discovery of a mycobacterial disease in wild armadillos recently captured in Louisiana. This disease could not be distinguished from experimental leprosy in armadillos by histopathologic, bacteriologic or immunologic criteria. The mycobacteria did not grow at 32°C or 37°C on Lowenstein-Jensen or 7H10 media.

In armadillos with this naturally acquired leprosy, there were large numbers of acid-fast bacilli (AFB) in macrophages of skin, ears, nerves, lymph nodes, liver, and spleen. Histopathologically, the lesions closely resembled lepromatous leprosy in man. The mucous membranes of the nose and mouth, and the tongue were often heavily infected. As in the eye of patients with lepromatous leprosy, there were AFB in phagocytes in the ciliary body and cornea.

Invasion of nerves by AFB is pathognomonic of leprosy in man, and in armadillos with naturally acquired leprosy, small nerves of the skin and large nerves (sciatic and brachial) contain many AFB within macrophages and Schwann cells.

In the indigenous disease, as in the experimental infection in armadillos and in leprosy in man, the AFB were well stained by the Fite-Faraco method and poorly stained by the Ziehl-Neelsen method. At the AFIP, we have found this staining property useful in differentiating *M. leprae* from other mycobacteria in histologic sections. The acid-fastness of the bacilli in smears or frozen sections was abolished by exposure to pyridine, as is the acid-fastness of *M. leprae* (Convit and Pinardi).

Lepromins of the Mitsuda-Hayashi-Wade type were prepared from five naturally infected armadillos and assayed in leprosy patients at the Institut Medical Evangelique, Kimpese, Zaire, by Staffan Kvernes, M.D., Carrie Stuart, M. D., and Edna M. Staple, S. R. N. The reactions read at four weeks corresponded to those obtained with lepromins prepared from human lepromas.

Thirty-five animals with indigenous leprosy have been discovered and studied by GSRI, and confirmatory tests have been done at the AFIP. The modes of infection and transmission of this disease have not been determined. By every test so far applied, the AFB in the tissues of these armadillos appear to be *M. leprae*. Assuming then that the AFB are *M. leprae*, we will speculate on the origin of this infection of armadillos and on its possible association with leprosy in man.

Leprosy has been endemic in man in southern Louisiana for more than 150 years. The armadillo appeared in Louisiana about 1926. In that era, there was no effective treatment for leprosy and all diagnosed patients were required to go to the USPHS Hospital at Carville, Louisiana. Some, however, evaded detection to avoid incarceration. Armadillos seeking food (particularly insects) could have come in contact with fomites from patients with active disease ; because of the high susceptibility of armadillos to infection with *M. leprae*, the disease may have established itself in local armadillos. The route of infection may be through wounds in the skin or by respiratory or gastro-instestinal tracts. Available epidemiologic data suggest that this may have happened in isolated areas, since several foci are far from other known centres of infection. Detailed surveys, however, are needed to construct a complete map of the distribution of indigenous leprosy in armadillos in Louisiana and in all areas inhabited by armadillos. The effective treatment of leprosy with sulfones, first reported

in 1943, came into general use several years later.

Another possibility is that *M. leprae* may be an unidentified soil bacterium found only in a suitable environment. This concept is reasonable since the distribution of nodules in the skin and nasal membranes of water buffalo with lepra bubalorum suggests that the infection is acquired from the mud in which the animals wallow.

Intensive epidemiologic studies of indigeneous leprosy in armadillos may contribute significantly to an understanding of the transmission of leprosy in man.

None of the experimentally infected armadillos from GSRI has escaped, so these could not be the source of the naturally acquired infection. Furthermore, the distribution of the natural infection is more widely dispersed in Louisiana than would be expected (up to 200 miles) during the five years that the armadillo has been experimentally infected.

Indigenous leprosy in armadillos makes it important that armadillos bred in captivity be used in future studies in leprosy. As yet, however, armadillos have not been bred in captivity. Only by the use of laboratory bred armadillos for the study of leprosy can the investigator be sure that the animal is free of naturally acquired leprosy. Until a supply of armadillos bred in captivity is available, armadillos to be used in experimental research in leprosy should be captured in a geographic area free of indigenous leprosy or be born of females that were pregnant when captured.

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CLASSIFICATION

D. S. RIDLEY

What, one may ask, is there special about leprosy that has made its classification a contentious issue? Why classify at all? Interest goes back to the early realization that while some patients had lesions with vast numbers of leprosy bacilli, of which they excreted millions a day, others had a disease with few bacilli or, apparently, none; yet they might have both paralysis and deformity. The variety of manifestations was remarkable. Not surprisingly, the first classification of leprosy was two types, skin and neural. It is now almost self evident that the number of bacilli which a patient harbours is dependent on his immunity. Although modern drugs kill leprosy bacilli they are unable to diminish their numbers; only the patients immunity can do that. And as we shall see later, nerve involvement is indirectly due to the immune mechanism also.

What is special about leprosy, therefore, is that it is the first infection in which a broad-ranging pattern of disease has been recognised as due to a broad-ranging immunological relationship between the patient and the infective agent, in this case the leprosy bacillus.

The Spectrum

Leprosy remains the classic example of an infection with a broad disease spectrum, but as a result of its study other infections are coming to be recognised as displaying a spectrum also, tuberculosis for example. However, tuberculosis, like the majority of infections, differs from leprosy in that it is due to an organism that is highly virulent to the patient. Either the patient has moderate immunity or he dies. The spectrum is narrow. By contrast, the leprosy bacillus in itself is remarkably non-toxic, and when immunity is low the patient is able to tolerate enormous numbers of the bacilli without suffering grievous damage. Eventually, of course, the unrestrained multiplication of the bacilli presents a problem that is difficult to treat, as well as presenting a hazard for the spread of infection to others. But the leprosy bacillus only becomes acutely damaging when the patient becomes hypersensitive to it, and the nerve, perhaps, where the bacilli have lodged, is destroyed as a result. "Delayed" hypersensitivity, which is the cause of most of the symptoms of tuberculoid leprosy, is closely related to immunity. If immunity

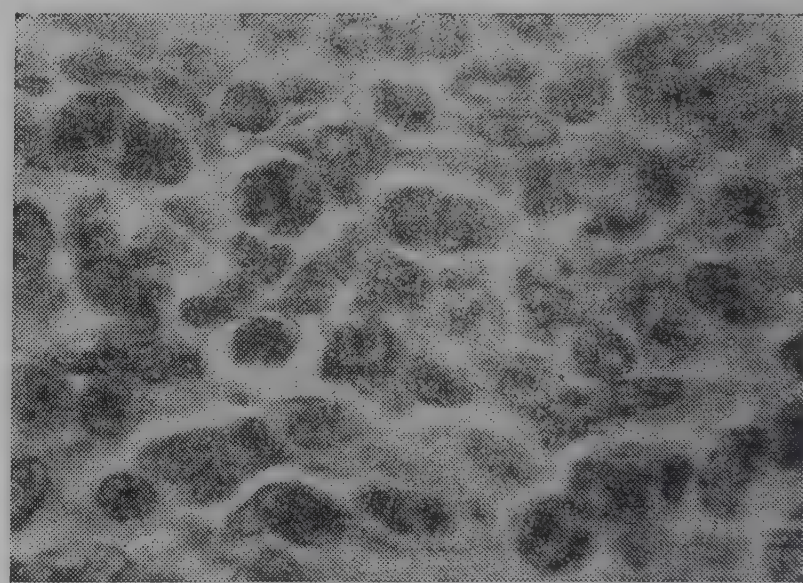


Fig A. In lepromatous leprosy the macrophages that ingest and ought to deotroy invading bacteria serve as the ideal host to the leprosy bacillus. The bacilli thrive and multiply. So do the macrophages.

is very high the patient will never develop leprosy, or it will be self-healing. But if immunity is moderately high, though insufficient to prevent the disease developing, then hypersensitivity is usually unavoidable. This on the one hand, and on the other a lack of immunity specifically to the leprosy bacillus (not other bacilli) are the twin bases of tuberculoid and lepromatous leprosy which clinically, pathologically and immunologically are so far apart. In between these two poles is the borderline region of the spectrum. The nearer to the middle of this region one goes fewer the patients one finds. This is not because mid-spectrum disease is rare, but because the disease in this situation is particularly unstable, and patients accordingly

are prone to move in the direction of the lepromatous or tuberculoid poles, with a corresponding change in their immunological state. This, of course, may have important implications for the patient, and may affect his treatment, just as treatment will probably affect the direction of the move in the spectrum. What happens is that when the immune state, the balance between immunity and bacteria, is upset there is often a temporary increase in hypersensitivity which is seen as a reaction. This happens most often in borderline patients on treatment. By contrast, the polar forms of leprosy are much more stable. A lepromatous or tuberculoid patient is less likely to change his classification to a group in some other part of the spectrum. However, this raises an important point. The majority of lepromatous and tuberculoid patients are not completely polar, situated at the extreme ends of the spectrum; rather, they are sub-polar; their position being near one or other of the two ends. Clinically, they will appear lepromatous or tuberculoid and this is what they are for most purposes. But, unlike the polar cases, they will be at some risk of moving across the spectrum with the possibility of hypersensitivity reaction, though the risk is much less than it is with mid-borderline patients.

There is, therefore, good reason for saying that leprosy is a disease consisting of two main types, and that the intervening borderline forms are less important because they are unstable and so, less common. The trouble is that if one lumps the majority of patients into the two main types, which it is quite easy to do, then these types become mixed bags in which are included a number of patients who will disobey whatever rules may be prescribed. Sometimes a crude lumping together is enough. Sometimes it is confusing, or conceivably harmful to the patient.

The Object and the Means of Classification

It is the position of a patient in the spectrum of leprosy that governs his response to treatment, his long term prognosis and risk of relapse, his liability to damaging nerve reactions or to erythema nodosum leprosum (ENL), and his infectivity. This, therefore, is the reason for and the object of classification. On this basis classification indicates prognosis. Most people are now agreed about this, but it has not always been so. It is only during the last 20 or 30 years that the idea of the spectrum has been fully accepted. And before then there was no effective treatment. At the time of the Cairo conference in 1938 it seemed sensible to use classification to register the advance of the disease, which was regarded as being of two types. Now that leprosy can be treated, and the response to treatment depends almost entirely on the position in the spectrum, it is sensible (and simpler) to make the spectrum the sole criterion of classification. But although this objective seems clear, the means of bringing it about is another matter. From what has been said, it would seem clear that the ideal means of classification would be a simple immunological test, a skin test for example. The lepromin test has its uses, but there is, as yet, no direct way of assessing the immune state of leprosy patients across the whole of the spectrum. The lymphocyte transformation test, which in any case is too complex for routine use, has been found to fluctuate too much during reactions. The most accurate available means at present is histology. The reason for this is that immunity in leprosy is mediated by inflammatory cells, and these cells can be directly observed in a skin biopsy. Histology in turn, has been correlated with immunological transformation. The result has been very useful as a means of evaluating systems of classification, and as a research procedure, and for classifying individual patients in selected cases. But as a routine for general use histology is not practicable. There remains the clinical picture, which is useful and has advantages of its own, and which can be correlated to some extent with histology though not completely. It must be read in conjunction with the bacteriological findings and the lepromin test. This is not altogether satisfactory but it is the present position.

The clinical and histological pictures are the means, not the object of classification. The means (clinical or histology) which, for convenience, has to be regarded as primary should not be regarded as exclusive. Classification may have to be made on limited evidence, but no evidence that has a bearing on the immune state of the patient should be ignored. The more the information available, the more accurate the classification.

Signs that indicate the Immune State and Sings that do not

If the object of classification is to assess the immune state by reference to clinical and histological appearances, one has to ask if immunity is the only factor that determines

these appearances. If it is not, there must be some aspects of the clinical and histological pictures that have to be discounted from an assessment of classification.

The clinical and histological pictures are brought about by inflammation caused by the leprosy bacillus, and the most important influence on the nature of this inflammation is immunity. But there are three other factors that influence the picture, all of which are somewhat related to immunity though distinct from it. One is the activity of the infection at a particular moment, another is the degree of advancement of the disease, and the third is reactions.

(1) The infection is active when it is out of control and the disease is spreading. Activity is seen as a more acute form of inflammation and clinically it presents mainly as erythema of the lesions. Can this be taken to indicate a failure of immunity? Obviously all leprosy represents a failure of immunity. But lepromatous infections are quite beyond the control of the immune system and so indicate a further deterioration in the immune state. It only indicates lack of effective treatment. On the other hand in tuberculoid leprosy, which is not yet altogether out of control and which in early cases may be self-healing, activity indicates the failure of immunity to restrain the spread of disease. An active maculo-anaesthetic or TT lesion may still be classified as maculo-anaesthetic or TT because it will still respond to treatment like other patients in the same group. But the activity is a warning that immunity is losing its grip and that without treatment the immune state may eventually deteriorate. In tuberculoid leprosy and in early lesions activity modifies the progress and must be taken note of in classification.

(2) Advancement of the disease is the usual outcome when an infection has been active for some time. Immunity directly affects the *manner* in which the disease spreads and this can be well observed clinically in a number of ways, e.g. the number and distribution of the lesions and the sharpness of their edges. But the *extent* to which lesions have developed (macule, infiltration or nodule) carries a question mark over its interpretation in the same way as does activity. It may or may not be significant, and for the same reasons. Any type of leprosy may start with macules, but not all end up with nodules. Nodules exclude the tuberculoid type. But if leprosy is lepromatous the form of the lesions merely indicates how far the disease has advanced. This may be of some importance but it is nothing to do with immunity, because any lepromatous infection will advance if it is not treated.

(3) Reactions cause acute inflammation and so they have to be distinguished from activity. They are the outcome of the immune state, not the cause of it. And so although the type of reaction depends partly on the classification of the patient the signs which indicate a reaction must be ignored when classifying a patient.

The Meaning of the Histological Picture

Granuloma. A section of a leprosy lesion may show solid clumps or accumulations of cells derived form the monocytes of the blood. These cells are phagocytic and ingest *M. leprae.* Having done so they are immobilised and form the clumps of cells known as granuloma. A granuloma is present in every established lesion, and is the site where the most leprosy bacilli are found. The number of bacilli in a granuloma is related to immunity. The size of the granuloma is not so related.

Macrophages and epithelioid cells. When monocytes ingest *M. leprae* they evolve either as macrophages when immunity is low, or as epithelioid cells when immunity is high or moderate. A granuloma, therefore, is composed of one or other of these two cell types, which can be identified. This immediately puts the patient in the upper or lower half of the spectrum.

Inflammatory cells. Besides the granuloma there are usually a number of lymphocytes or plasma cells (and in ENL neutrophil polymorphs). These are the inflammatory cells. In early lesions or macules, lymphocytes and plasma cells may be the only cells present, with no granuloma. This makes histological classification much more difficult. Lymphocytes and plasma cells do not ingest *M. leprae* and so they are less useful in classification. However, some sorts of lymphocytes transmit immunity to macrophages which is important, while plasma cells produce humoral antibody which is of significance mainly in ENL. Plasma cells are scanty in tuberculoid leprosy. Lymphocytes are numerous in the lesions in some parts of the spectrum, and they are a sign which is favourable to the patient.

Protected sites. If no granuloma is found in an early lesion after a thorough search,

the bacilli must be present somewhere else. When immunity is high and the bacilli have not yet established themselves they do not survive in those sites in which they multiply freely when immunity is low. Instead, they are to be found at certain 'protected sites', in which they appear not to be readily detected by the immune mechanism. This happens either in early leprosy or in established tuberculoid leprosy. The most important protected site is nerve, especially the Schwann cell, and the second most important site is the subepidermal zone of the skin. These two sites are the places to look for bacilli in early lesions or in tuberculoid infections. Being immunologically undetected they are able to multiply to the point at which they become detected. Then, if immunity is high and hypersensitivity has developed there will be a violent cellular response. The bacillus is usually destroyed and so is the nerve. The nerve becomes swollen and the sub-epidermal zone is invaded by the infiltration and multiplication of epithelioid cells. Thus a swollen nerve bundle or the absence of a clear sub-epidermal zone both mean the same thing, namely that there has been a hypersensitivity reaction to a bacillus and immunity must be high. On the other hand a relatively normal nerve or a clear sub-epidermal zone might mean, if bacilli are scanty, that no bacillus has happened to lodge in that position. This is not very useful. However, if bacilli are numerous a normal nerve or clear sub-epidermal zone means that the infection is lepromatous.

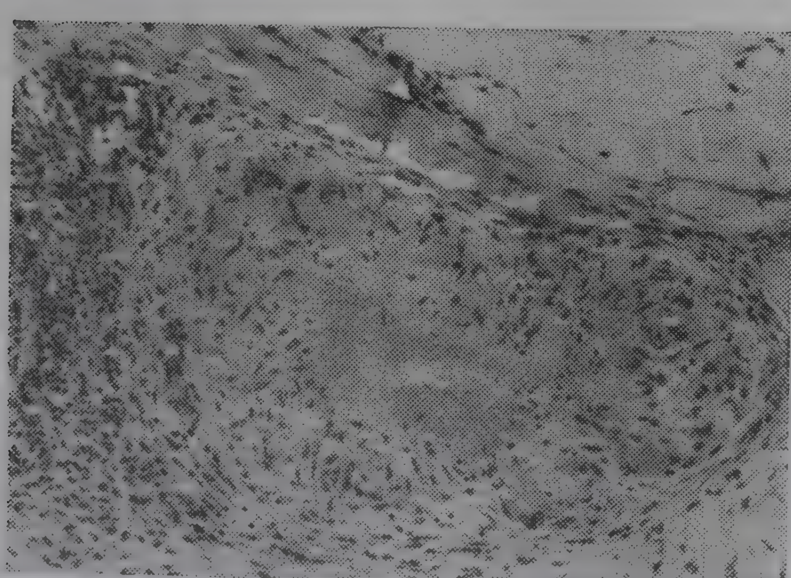


Fig. B. Destruction of a protected site (a nerve bundle in the skin) when hypersensitivity is very high (TT) and a few bacilli have become detected. Note the epithelioid cell granuloma with a necrotic, caseous centre. Some of the giant cells here are typical of the Langhans variety.

Signs of hypersensitivity. We have already mentioned that epithelioid cells in nerve or sub-epidermal zone indicate hypersensitivity. An even more striking sign of severe hypersensitivity is the presence in a granuloma of numerous large giant cells of the Langhans variety. These cells have multiple nuclei around the periphery of the giant cell, the centre of the cell being clear and solid with no vacuole. Another sign of maximum hypersensitivity, not often seen, is a patch of fibrinoid necrosis in the collagen of the dermis, or of caseation in the centre of a nerve bundle (nerve abscess). In leprosy the sort of caseation that is common in tuberculosis occurs only in nerve bundles.

Fig C. Preservation of a protected site (sub-epidermal zone) when hypersensitivity is less then maximum (TT). This might be because bacilli in the clear zone have not yet been detected, or because there are none there. Deeper down, nearer the blood vessels, bacilli grow more readily but they are easily etected. A granuloma has developed. The giant cells are too small for Langhans cells.

I have described and illustrated the histology of leprosy more fully in a booklet, "Skin Biopsy in Leprosy", produced by Documenta Geigy.

The Meaning of the Clinical Picture

When trying to interpret the clinical picture and correlate it with histology, it must be remembered that there is usually a delay of 2 or 3 months before a pathological process seen in a biopsy makes its impression on the clinical picture. The clinical classification, therefore, in a patient in the unstable part of the spectrum may be in arrear of the histological classification. Apart from this, some lesions may retain their old appearence for months and years after the classification has changed, though new lesions will indicate the present

situation. The mixed types of lesion are a clue to the history of the infection which is not seen by histology, and it is this that gave rise to the concept of dimorphous leprosy.

Some clinical signs can be correlated with the pathological process that causes them, and be understood accordingly. Others such as the form and shape and size of lesions are often more difficult to explain or understand; but since these are the signs that first strike the eye they will be considered first.

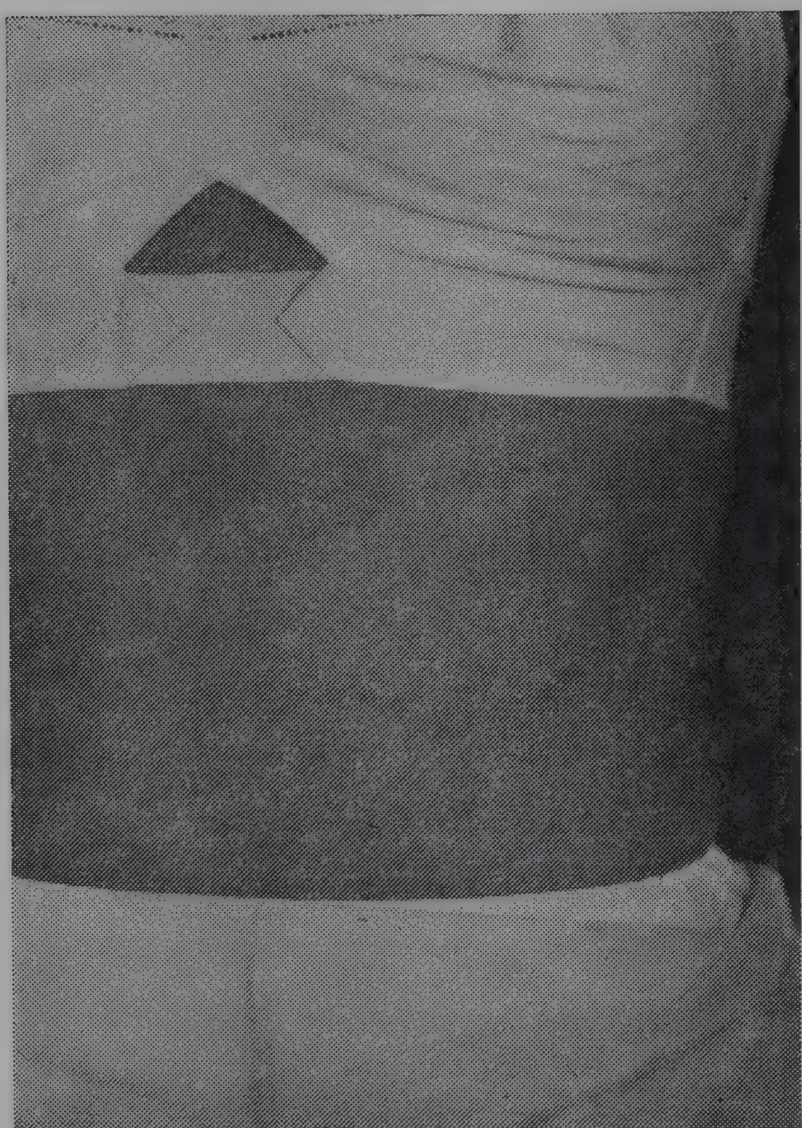


Fig D. Indeterminate leprosy. This solitary hypopigmented macule is certainly leprosy because there was in addition an enlarged nerve. This and the fairly sharp edge suggest it may be tuberculoid, but there was no anaesthesia. In is not, therefore, classifiable. (Photo, Dr. W.H. Jopling).

Macules are flat, and distinguished only because their colour is different from that of the surrounding skin. In this type of lesion there is extremely little granuloma and not much cellular infiltrate, and so a macule is not palpable. Because a granuloma may not be found, histological classification of macules is often less helpful than the clinical picture. Even though a macule may persist for years the lesion is still "early" in that it has not fully developed or evolved. Such lesions may be found in any part of the spectrum.

Plaques and all other skin lesions apart from macules are the clinical counterparts of lesions with a definite granuloma. The reason why they take the form that they do take is not always apparent. Plaques have a raised surface and they are found throughout the spectrum except at the extreme lepromatous pole. In tuberculoid cases immunity restrains the heaping up of the lesion except at the active edge, so that the lesion is fairly flat with a broad depression at the centre. Descending the spectrum one finds first a heavily heaped-up rim (annular lesion) and then, in the middle of the spectrum, more profuse heaping up with only a punched out centre.

Papules and nodules are found only towards the lepromatous end of the spectrum. In lepromatous patients they are full and rounded but in those who are somewhat borderline nodules may be dimpled. Infiltration is another form of lesion that is predominantly lepromatous.

Erythema indicates acute inflammation due to activity or reaction. Because erythema is seen best in a pale skin or hypopigmented patch, and because macules are hypopigmented more often than nodules or infiltrated areas, erythema is best seen in macules, though these are not necessarily the most active lesions. Untreated lepromas are always active. In untreated tuberculoid patients activity indicates some loss of immune control.

Surface of the lesions. Tuberculoid plaques have a rough pebbly surface in many cases, though this does not apply to macules. A smooth, shiny and succulent surface indicates an unrestrained advance of the disease, which can only be lepromatous.

Distribution and spread of lesions. The number and distribution of the lesions and the sharpness of their edges are some of the most valuable clinical signs employed in the classification of leprosy. In lepromatous patients the infection is able to spread via the blood stream. The lesions, therefore, are many and they are almost exactly bilaterally symmetrical. Their edges are vague owing to the uninhibited invasion of the surrounding tissue. In borderline patients blood dissemination is partially restricted. In tuberculoid leprosy immunity is strong enough to prevent blood stream spread except possibly

from nerve to nerve. Lesions, therefore, are few, asymmetrical and their edges are sharply demarcated. However, they may reach a large size in the course of time because, though they cannot leap, they can slowly grow.

Dry, hairless skin. The sweat glands and hair follicles are downgrowths of the epidermis. Their destruction by the inflammatory process in leprosy, resulting in a dry hairless skin lesion, has exactly the same significance as the invasion of the subepidermal zone and epidermis already described. But whereas a histological section often provides a better view of the epidermis than the glands and follicles, clinically one gets a very good impression when a skin lesion is dry and hairless. This only occurs near the tuberculoid end of the spectrum, and is a very useful clinical sign.

Anaesthesia of skin lesions or partial loss of sensation obviously indicates destruction of nerve and is a very important feature of tuberculoid leprosy, in which anaesthesia may be complete even in the early stage. Muscle weakness has the same significance. These signs may occur in more lepromatous lesions if the disease has evolved (downgraded) from the tuberculoid form, and then loss of sensation is only partial. In late lepromatous disease there may be some degree of anaesthesia or analgesia and some weakness due to fibrosis of nerves. Where innervation is very rich, as on the face, anaesthesia of lesions is not so complete as it would be in areas where there is less overlap of the nerve supply.

Enlargement of nerves seen clinically is usually due to swelling with epithelioid cells. The swelling is greatest in tuberculoid leprosy, in which a swollen peripheral nerve may even be visible, and gets less as one descends through the borderline region of the spectrum. The fibrosis of late lepromatous leprosy produces only a slight swelling. But whereas the swelling of individual nerves diminishes in a gradient from tuberculoid to lepromatous, the number of the affected nerves increases correspondingly. Reactivity is less, freedom of spread is greater. Thus nerve enlargement is in line with skin involvement. Both are generally larger but fewer near the tuberculoid pole, smaller but more numerous towards the lepromatous end.

Polyneuritic leprosy. Khanolkar taught that all leprosy was neural in its inception. Equally, sooner or later all leprosy "breaks-out" from nerve into skin once the leprosy bacillus has established itself in the body and is able to multiply in non-protected sites. But the stage in the disease at which the break-out occurs is variable and some patients go through a period of nerve involvement with no perceptible skin lesions. In tuberculoid leprosy this is understandable. But multiple nerve involvement without skin lesions poses a paradox, since a preference for nerves is a tuberculoid feature, while involvement of many nerves is a non-tuberculoid feature. The explanation is that the polyneuritic patient has to some extent evolved from tuberculoid to borderline or near leproma before the the break-out into skin has taken place. Why should this be? We do not really know but we can surmise that it is partly a matter of chance, once dissemination of bacilli via the blood stream becomes possible, whether the secondary site is in skin or another nerve. Perhaps more important, nerve is not the only protected site. If bacilli find their way to the epidermal region in the early stage of the disease, and multiply there before they are immunologically detected, a skin lesion is certain to follow. If bacilli do not gain access to the epidermal region the infection is more likely to go through a neuritic phase. Thus the occurrence of the neuritic phase may well depend also on the route by which the infection is transmitted from person to person as well as the route of dissemination within the body. Polyneuritic leprosy is never completely lepromatous. But it can be classified within the tuberculoid and borderline parts of the spectrum in the same way as leprosy with mixed nerve and skin lesions.

Facial involvement. Advanced lesions of the face and nose only occur in true lepromatous leprosy. The signs include the leonine face with deep lines on the forehead, thickening of nose and ears, thinning or loss of eyebrows and eyelashes, keratitis and iritis, loss of incisor teeth, saddle nose deformity, and in active cases, a heavy load of bacilli in the nasal mucosa. Testicular atrophy is another sign of a fully developed lepromatous infection.

Indeterminate or Classifiable?

Most of what we have said so far is concerned with leprosy that has progressed and evolved far enough to become classifiable. Obviously, however, there must be an early phase when the disease is recognisable as leprosy but is not yet classifiable with any confidence. The clinical and histological pictures, together or singly, have not yet

acquired sufficient detail to be distinctive. This is indeterminate leprosy. It cannot be defined except to say that there are one or several macules but that the evidence necessary for proper classification is vague or lacking. Even so, if the patient was lepromin positive it would be safe to say that he was non-lepromatous, and if some bacilli were found that he was non-tuberculoid. The important point is to realize that the indeterminate group (or better, non-group) is not part of the spectrum.

Indeterminate leprosy is often in the course of evolving. On the other hand it may persist for a long time without change or it may heal spontaneously. Much as one would like to know the outcome there is nothing one can do except to examine patients so carefully that as many as possible are classified within the spectrum. The form from which indeterminate has to be distinguished most commonly is maculo-anaesthetic leprosy; but before discussing this it is better to look at the systems of classification now in use.

Systems of Classification

There are four systems of classification in common use at present. All recognise the indeterminate group. They divide the spectrum into 2 groups (lepromatous and non-lepromatous), 3 groups plus sub-groups (Madrid classification) or 5 groups (Indian classification and the Ridley-Jopling system). The Ridley-Jopling classification will be described first as it gives the best correlation with immunity. Apart from indeterminate, the spectrum, which of course is continuous, is divided for convenience into 5 more or less equally spaced groups: TT (polar tuberculoid), BT (borderline tuberculoid), BB (mid-spectrum borderline) BL (borderline lepromatous) and LL (lepromatous). For a full account and illustrations it is best to consult the paper in the International Journal of Leprosy of 1966, but the clinical side of the classification can be summarized well enough in a Table which is based on the work of Dr. W. H. Jopling, to whom also I am gratefully indebted for kindly supplying all the clinical illustrations in this chapter. Confirmation or correlation by histology is needed for research, but that need not concern us here.

Other systems of classification are simpler in some ways than the Ridley-Jopling scale, and it would be an advantage if they could be correlated with it. The problem is that they are simpler in the main because they rely largely on clinical signs which are chosen because they are easy to observe, not because they correlate well with immunity; in particular these are the flatness or elevation of the lesions, which correlate mainly with the progression of the disease and increase of the granuloma. The correlation of alternative systems therefore, is imprecise.

Fig. E. A solitary anaesthetic lesion with central flattenjng and a sharp edge. Classification TT. (Photo, Dr. W.H. Jopling).

The diagram indicates the usual correlations between the four systems, common and less common that would obtain in the majority of cases. The correlation between the Madrid and Indian classification presents no problem. The correlation of these with the Ridley-Jopling scale is moderately sucessful. On occasion there could be more glaring discrepancies; much depends on the skill of the clinician.

The Ridley/Jopling Scale (Clinical)

	TT	BT	BB	BL	LL
Form of lesions	Few macules and/or plaques. Plaques tend to be large, with rough, dry, hairless surface; well defined edges from which there is gentle slope to flattened centre.	Similar to TT. Differentiated by: (a) lesions more numerous, surface less dry and rough, edges less sharp; may be slight hair growth. (b) Annular lesions common, with heaped up rim which has sharp outer and inner margins.	Macules and plaques are intermediate in number and size between TT and LL. Punched out lesions are characteristic. Annular lesions occur as in BT.	Similar to LL. Differentiated by: (a) Macules and plaques not consistently small; edges less vague. (b) Punched out lesions sometimes present. (c) Papules and nodules few; nodules may be dimpled.	Macules, papules, nodules and plaques may all be present. Lesions numerous and small. Smooth shiny surface. Macules and plaques have vague edges. No hair loss.
Distribution of lesions	Asymmetrical	Asymmetrical	Asymmetrical	Small multiple lesions are bilaterally symmetrical. Older plaques not symmetrical.	Lesions nearly all bilaterally symmetrical. One or two old borderline lesions may be found; these are asymmetrical.
Anaesthesia of lesions	Marked anaesthesia.	Moderate anaesthesia.	Mild anaesthesia	There may be small patches of anaesthesia.	No anaesthesia.
Nerve thickening	Often single. May be first sign of disease.	More than one nerve affected, or several. May be first sign of disease.	More numerous in BT. May be first sign of disease.	Numerous. May be first sign of disease.	Only occurs late. Never first sign of disease. Tends to be symmetrical (eg. glove and stocking anaesthesia).

The Ridley/Jopling Scale (Clinical)—*Contd.*

	TT	BT	BB	BL	LL
Face	Not affected except for lesions	Not affected except for lesions	Not affected except for lesions	Occasionally there is slight iritis, keratitis, loss of eyebrows or thickened ear lobes	Except in early infections there is nasal ulceration, iritis, keratitis, loss of eyebrows and eyelashes and thickened ear lobes.
Lepromin test	Strongly positive	Moderate or weakly positive.	Negative	Negative	Negative
Bact. index	0/1	0/2	2/4	4/6	4/6
Prognosis without treatment	Early lesions self healing	Very early lesions may be self-healing. More likely to downgrade.	Quickly downgrades to LL	Downgrades to LL	Progressive advance without change in classification.
Fall bact. index 6 months with treatment	...	100%	78%	23%	10%
Hypersensitivity reactions	Rare	Fairly common	Usually	Fairly common	Rare
ENL	Never	Never	Never	Occasional, mild	Fairly common, often severe.

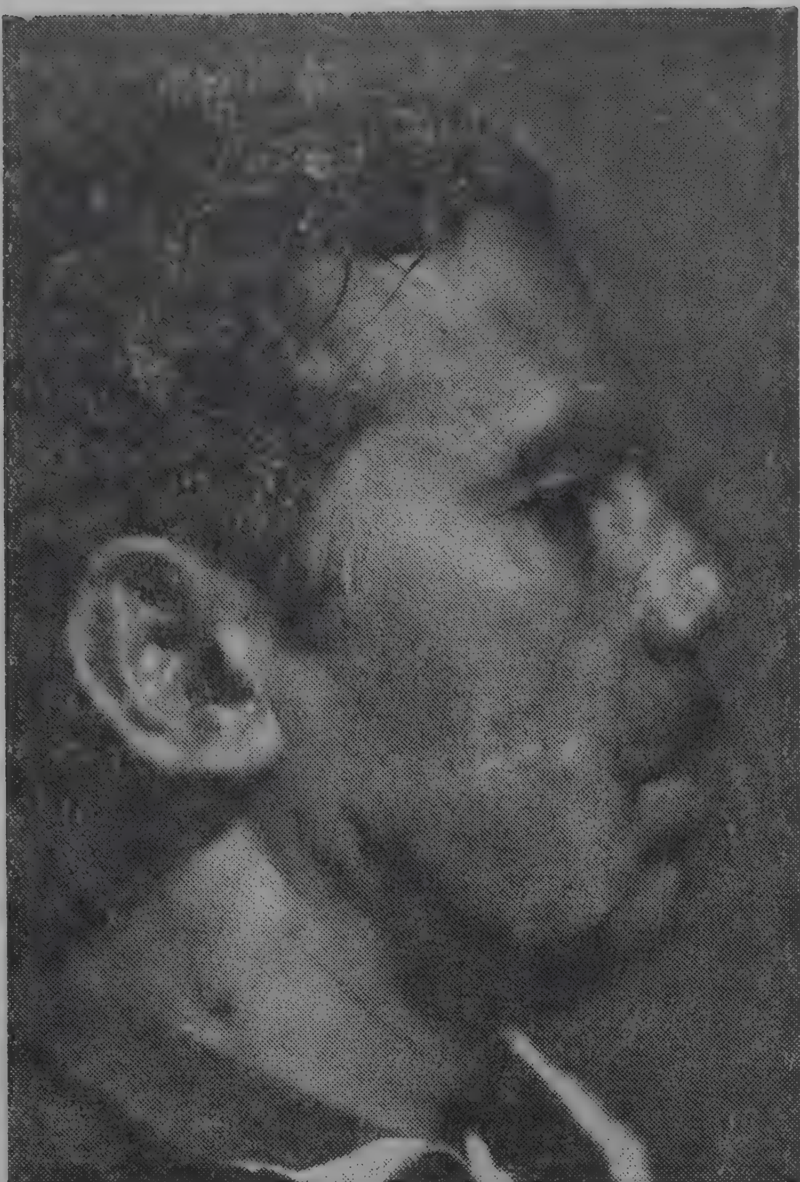


Fig F. This solitary, anaesthetic lesion with a visibly enlarged nerve in many ways looks like TT. But there is no central flattening. Classification BT. (Photo, Dr. W.H. Jopling).

Fig G. There are punched out lesions on the thigh with sharp inner and outer edges. Also an annular lesion on the elbow. Classification BT. (Photo, Dr. W.H. Jopling).

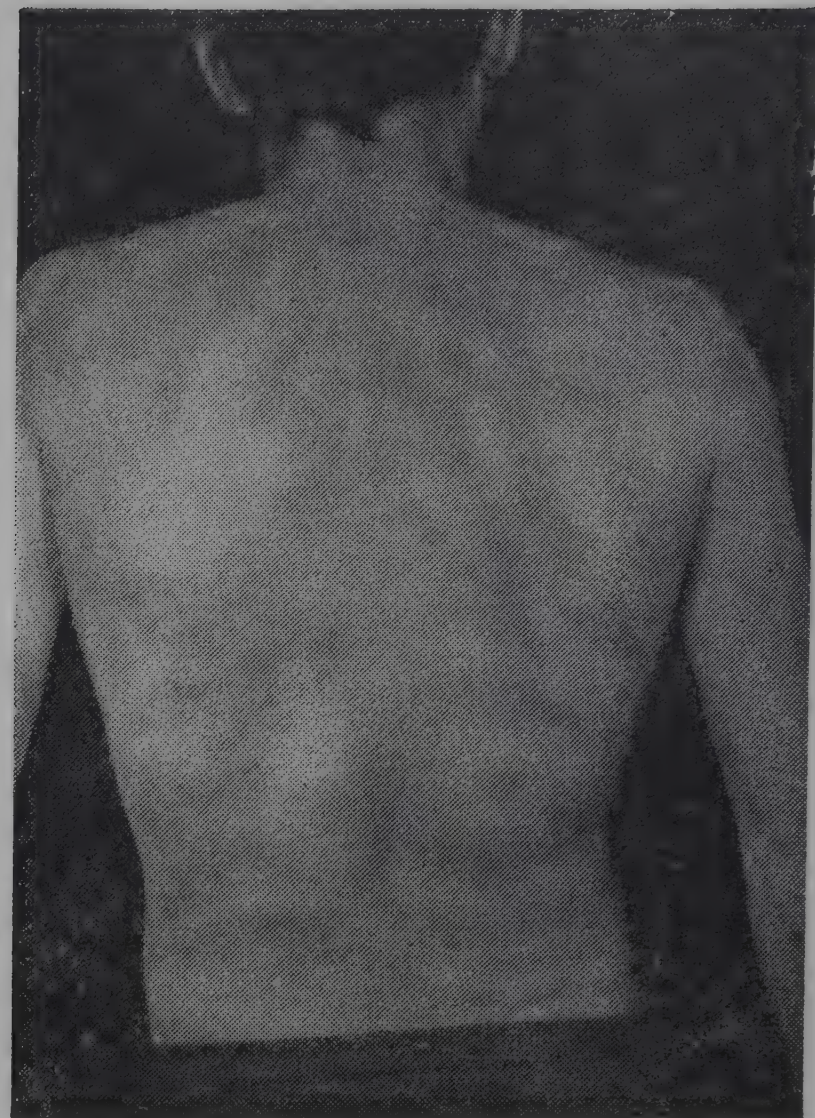


Fig. I. These lesions are both numerous and symmetrical. But they are altogether too large to be LL. Classification BL. (Photo, Dr. W.H. Jopling).

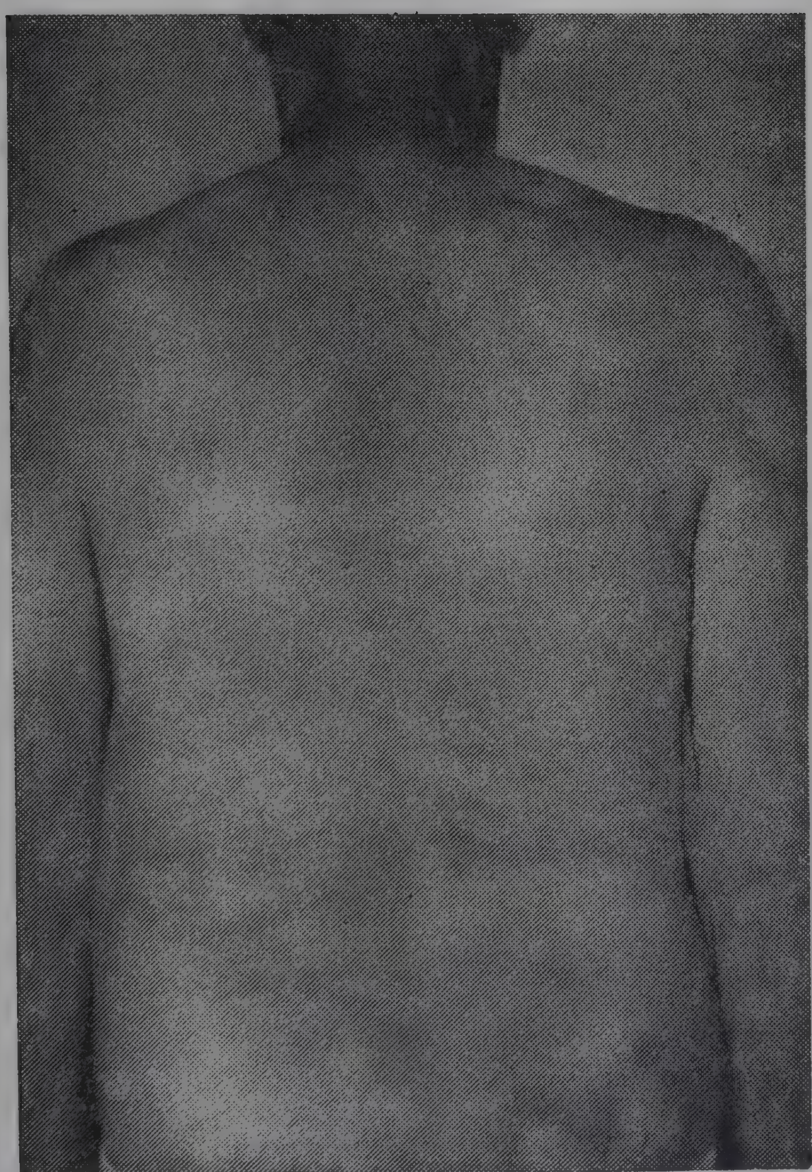


Fig H. Punched out lesions. Here the inner edges are sharp but the outer are much less sharp. Classification BB. (Photo, Dr. W.H. Jopling).

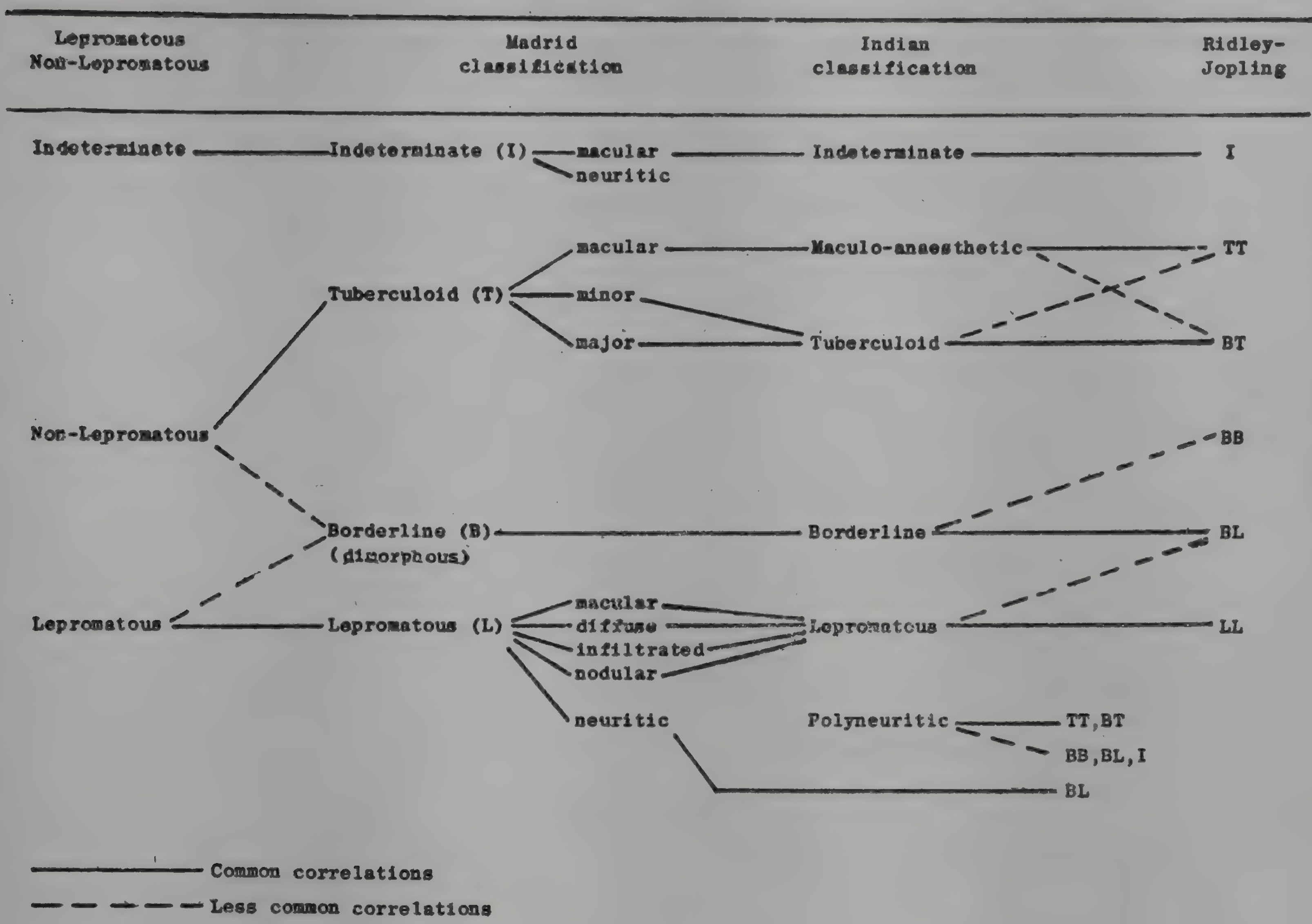
Fig J. Numerous, symmetrical, rounded papules and nodules. Classification LL. (Photo, Dr. W.H. Jopling).

Maculo-anaesthetic and Tuberculoid leprosy

Tuberculoid leprosy presents a special problem in classification because, whereas it cannot be classified until it is developed, the more tuberculoid it is the less likely it is to develop. The term tuberculoid was originally derived from the histological form of the developed lesion. Indian leprologists were the first to insist, quite rightly, that some macular lesions could be indentified as of the high immune (tuberculoid) type, and so distinguished from indeterminate, even though the lesions were not elevated and might not have a tuberculoid histology. These, of course, are "earlier" than fully developed lesions, and they may never develop. The likelihood is that they may be somewhat nearer the tuberculoid pole than the lesions that develop into plaques, though this is not necessarily the case because one does not know what the future evolution of a particular lesion might be. All one can say is that these maculo-anaesthetic lesions fall within the TT-BT region of the spectrum, and it seems likely that a majority are closer to TT than BT even though this may be difficult to confirm. However, the points of differentiation between TT and BT can be applied to maculo-anaesthetic lesions in the same way as to any other sort. If there is a point of confusion it is perhaps that immunity which is weak enough in some cases to allow some dissemination of lesions may nevertheless be adequate to induce self-healing. There are two possible explanations. One is that the disease is transmitted

Fig K. The numerous papules were symmetrical, though this cannot be seen in the photograph. This is LL. But the larger lesion on the cheek was not symmetrical. It is an old borderline lesion which indicates that the LL is of the secondary or sub-polar typc. (Photo. Dr. W.H. Jopling).

The relationships between the systems of classification



via a mucous membrane to the blood stream in some cases, and dissemination therefore, occurs at the inception of the disease. The other is that a build-up of immunity takes place after the infection has become disseminated.

Tuberculoid lesions that have fully evolved to the granulomatous stage, clinically elevated, are more likely to be BT than TT. Very few cases of the type originally described as TT, other than the macular variety, have ever been found. The majority of histologically TT lesions are those that have upgraded from BT in a hypersensitivity reaction. These remain clinically BT because their old lesions persist much longer clinically than they do histologically. Thus one would speak of primary and secondary TT. Similarly there is a primary and secondary form of LL. The secondary form, those that have downgraded from borderline, are not absolutely in the same polar position as the primary LL cases, though for ordinary purposes it is convenient to include them in the same group.

Conclusion: Which Classification?

Classification first and foremost is a means of communication. Obviously it would be a big advantage if there were only one system which was understood by all who have to treat leprosy patients or are professionally concerned with leprosy. Amongst other advantages this would make it easier to transmit the results of research to people in the field who would probably be the chief beneficiaries. The problem is that research workers require the relative exactness of the Ridley-Jopling scale. Those involved in the problems of field work require something simple, and it is unlikely that it will ever be possible to evolve a single system which is satisfactory for both purposes. Nevertheless we might hope that it would be possible to obtain a better correlation than exists at present. One might also ask whether the demand for simplicity is not sometimes due to a fear of making mistakes with two particular groups: indeterminate and borderline. One of these is not yet fully evolved, the other is evolved but unstable. Both are in a state

of change. Minor mistakes with classification are inevitable, partly because the spectrum is continuous, not a series of steps; partly because a patient's classification may change; and partly because for exactness histology would be necessary but is usually unavailable. Would it not be better to accept the risk of error (within limits) in the classification of the less stable patients than to insist on a system which though apparently fool-proof, creates problems by its lack of clarity, e.g. lepromatous-non-lepromatous? Until there is better agreement about the way ahead it is useful that there is a good correlation between the Madrid and Indian classifications. Each of these presents a workable compromise which could perhaps be improved upon by minor modifications.

THE DIAGNOSIS OF LEPROSY

S G BROWNE

Much has been made of the difficulties of diagnosing leprosy, mainly because of the extremely varied clinical picture presented, but in reality the vast majority of cases can be accurately diagnosed, and accurately classified, on clinical grounds alone. All that is needed is—two good observant eyes, a piece of cotton wool (or feather, or leaf) for testing for sensory loss, plus an accumulated picture memory, a sort of atlas of coloured transparencies, in the occipital cortex. Where leprosy is a rare disease, it is frequently not diagnosed simply because it is not thought of or suspected; where it is common, it may be overdiagnosed because the leprosy doctor or paramedical worker is insufficiently acquainted with non-leprous diseases of the skin.

Our advice would therefore be—

1. Think of leprosy

First, *think of leprosy* when taking a clinical history, which of course should include a family history and a geographical history ("Where have you been, and when?"). Think of leprosy when the history discloses some transient or persistent localized disturbance of sensation, some area of numbness, or of "pins and needles".

Think of leprosy when confronted by a skin lesion that doesn't quite conform to a well-known and well-recognized skin disease common in the locality, or a chronic condition that does not itch, and that does not respond to antifungal applications; furthermore, if the lesion is characterized by some loss of pigment, especially if the area of pigment loss corresponds to the area of sensory impairment, then leprosy is the likeliest diagnosis.

In parts of India, it is not uncommon for leprosy to install itself without any obvious changes in the skin, but the bacilli invade certain peripheral nerve trunks or smaller nerves and cause damage to fibres subserving motor and/or sensory functions. So-think of leprosy whenever confronted by signs of damage to peripheral nerve trunks for which there is no other obvious explanation. The commonest nerve affected is the ulnar, but almost any mixed peripheral nerve may show damage. The evidence of this damage is to be found (as would be expected) in the area of distribution of the nerve, that is the muscles supplied and the skin innervated, and also in the nerve trunk itself. At certain sites of predilection, such as just above the elbow, or around the head of the fibula, the nerve trunk is tender on palpation, and may be enlarged and harder than normal.

Signs of nerve involvement, of course, may follow the skin manifestations of any kind of established leprosy, but the diagnosis is then suggested by the skin lesions themselves and confirmed by the presence of the typical signs of nerve damage.

A word of warning is not amiss: far too often leprosy remains undiagnosed because the patient or the paramedical worker or the doctor cannot find obvious signs of nerve damage. This is really inexcusable. Another word of warning: every tender nerve trunk is not leprous; superficial nerves may be palpable in the thin, spare Indian, and constant friction may result in tenderness and perhaps enlargement.

2. Know the common presentations of leprosy

The skin lesions of leprosy may present a bewildering variety of macules, papules, nodules, plaques, bizarre circinnate lesions, different combinations of hypochromia, dyschromia and hyperpigmentation, diverse disturbances of sweating and hair growth, etc. There is no easy way, except a long apprenticeship, to gain this knowledge. Whole population surveys in areas of high prevalence,

contact examination, careful clinical followup of all patients under treatment, attendance at a Skin Clinic to learn the diagnostic features of the dermatoses locally common—all this would provide a sound basis.

A good light is as necessary as a good teacher, for some early lesions are discernible with difficulty and only in good oblique light. Close observation of the skin surface, preferably with a magnifying loupe, will disclose details of disturbance of pigment and sweating, broken or lost hairs, alteration of the appearance of the epidermis, and evidence of scarring in the dermis.

As far as possible, when building up a body of knowledge necessary to the diagnosis of leprosy, the novice (doctor or nurse or paramedical worker) should appreciate the pathological basis for diagnosis and classification. Today this means essentially some acquaintance with the rudiments of microbiology, histopathology and immunology—sufficient to understand the processes that produce the manifestations that form the "grist to the mill" of diagnosis.

The patient may present with one or other of the classical manifestations of leprosy in a readily classifiable form—indeterminate, tuberculoid, borderline or lepromatous—or may be hiding his real fears and signs in skin or nerves, and complain of some unrelated condition. Or he may produce some unusual sign that is worrying him—such as, impairment of vision, epistaxis, painless burn or wound, chronic ulcer of the foot, loss of upper incisor teeth, stuffiness of the nose—the list is well-nigh endless.

Know the various disguises under which leprosy may masquerade, and its commoner presentations, confirm your clinical suspicion with appropriate tests and investigations—and you will correctly diagnose the vast majority of patients with leprosy.

3. Learn about the conditions that frequently mimic leprosy

Leprosy vies with syphilis as the great imitator. Many cases of leprosy are missed, perhaps for years, and perhaps by skin specialists, because leprosy looks like some other disease. The more you know about other diseases of the skin and the peripheral nerves particularly, the fewer diagnostic errors you will make—in the sense of diagnosing leprosy when it is something else, and of diagnosing something else when it is really leprosy.

There are skin conditions that occur at certain seasons, or when climatic conditions (sun, dryness of the atmosphere, humidity, wind, etc.) are propitious. Other changes in the skin follow dietary deficiencies. Many congenital or acquired disturbances in skin pigmentation should be recognized. Other causes of depigmentation, due to fungal infection, the treponematoses, and parasitic infections like onchocerciasis, may be far commoner in certain areas than the typical hypopigmented lesions of leprosy.

Periodic attendance at a good skin clinic will alert the unwary to the many pitfalls in the differential diagnosis of leprosy; and attendance at a general orthopaedic clinic or a neurological clinic will reveal many of the other conditions that may result in the changes due to motor and sensory deficit that leprosy workers see in their patients. Diabetic neuropathy, peripheral vascular disease, tabes dorsalis—and many other toxic, infective or degenerative conditions may result in clinical pictures closely resembling those found in patients suffering from leprosy.

4. Look for the cardinal, positive signs of leprosy

a. Clinical

These are primarily clinical, and concern the typical characteristic appearance of lesions of the skin and nerves. In these days of sophisticated laboratory investigations, it is reassuring to know that leprosy can usually be diagnosed with confidence by a well-trained clinician.

If, in addition to the appearance of the typical skin lesions, there is sensory disturbance within the area of altered appearance, the suspicion of leprosy is confirmed. If one or other peripheral nerve trunk—in relation or not to the skin lesion—shows typical deviations from the normal, leprosy is even more likely.

b. Microbiological

The presence of acid-alcohol fast bacilli of typical morphology and typical distribution in smears of the dermis, or nasal mucus (or mucosa) taken by a trained technician according to a standardized technique, and fixed and stained and read competently, is diagnostic of leprosy.

c. Histopathological

If such bacilli are not found at the sites indicated, the diagnosis of leprosy is by no means excluded, for they cannot be found by such techniques in the great majority of patients suffering from indeterminate or tuberculoid leprosy. It is in these cases that histopathology may help. In the case of indeterminate leprosy, the histopathological picture may be suggestive; and if time permits (and that means several hours available for detailed examination of serial sections), acid-alcohol-fast bacilli, whole or fragmented, can usually be found, most often in neural tissue in the dermis. In tuberculoid leprosy, the microscopical picture is typical, and frequently diagnostic. In early lepromatous leprosy, a delimited area may often be revealed in which bacilli (perhaps in globi) are found. The concentration may be insufficient for their detection by the haphazard methods of skin smearing.

d. Immunological

The lepromin test is very rarely of any diagnostic help; perhaps in the case of a patient with a skin lesion resembling tuberculoid leprosy whose lepromin reaction happens to be negative—the test will exclude leprosy and open the diagnostic field to such conditions as tinea marginata.

With these four points in mind, the clinician may confidently approach the dangerous and difficult area, bestrewn with pitfalls innumerable and with deceptive hazards, of the diagnosis of leprosy.

Diagnosis of early lesions

As more and more areas in India are becoming leprosy-conscious with the work of SET programmes and diagnostic teams, it is to be hoped that once the backlog of established and longstanding leprosy has been recorded and dealt with, successive surveys and contact examinations will disclose many cases of leprosy at the earliest clinically detectable stages.

Before that stage is reached, however, and whenever prevalence rates exceed 1 per 1,000, it must be assumed that the great majority of people have been exposed to leprosy infection. Most of them will have been exposed to viable leprosy bacilli in inadequate numbers or for too short a time for infection to have occurred. Another group comprises subjects who have been exposed for long periods to massive concentrations of leprosy bacilli; these would include members of families where there is a case of multibacillary leprosy not under treatment, and medical staff in daily contact with leprosy patients. Most of these exposed persons will have contracted subclinical forms of leprosy—with no signs or symptoms, but tell-tale changes in the lymphocytes. Obviously, there are no grounds for the diagnosis of leprosy in these close contacts, no need for treatment, and little possibility of clinically diagnosable leprosy supervening.

In addition to the above groups of persons exposed to leprosy infection, but not succumbing to it, there are others whose natural defences (that is, lymphocytes specially concerned with defending the body against certain types of micro-organisms) are not sufficient absolutely to prevent the multiplication and spread of the leprosy germs in the tissues. As yet, there is nothing in the appearance of the skin to suggest that all is not well; in fact, the individual looks well, and feels well. But he is in the incubation period of leprosy. This period may be long, or not so long; it is commonly three to five years; it may be somewhat shorter, or it may possibly be much longer. The old books that referred to "premonitory signs" were attributing to leprosy such common and non-specific symptoms as diarrhoea and headache, bouts of fever and such like. The only way of discovering if, among the people exposed repeatedly to leprosy infection (usually in the household), there are those who will probably develop recognizable signs of the disease within a few years, is to examine skin scrapes (from the dermis) and, by concentration techniques, demonstrate typical leprosy bacilli. From the apparently normal skin, then, such as the ear-lobes or anywhere else, it is possible in these individuals to find living multiplying leprosy bacilli. A suspension of these bacilli can be made, and the suspension injected into the footpads of mice to confirm the suspicion that they are indeed leprosy bacilli. Of course, it is not possible to do this examination routinely, in case-finding campaigns, but these results of research should remind us that the leprosy germs do enter the body of people in contact with sufferers from certain kinds of leprosy, untreated. And if the cellular defence of these contacts is not adequate, they will sooner or later succumb to leprosy infection. Fortunately, the great majority of people have

some degree of defence, and do not catch leprosy.

The next group includes all those with early leprosy lesions that will resolve completely and spontaneously, without treatment. The frequency of this form of leprosy may remain completely unsuspected—until whole-population surveys are done at frequent intervals. Then, many people are found to have one or a very few areas of slightly hypopigmented skin, ill-defined, difficult to see (except in a good light). These lesions do not irritate. There are usually no disturbances of sensation or of sweating. Leprosy bacilli are not found by standard methods of examination (slit-smear or histological), but they are present, very scanty, and confined to neural tissue in areas showing patchy (focalized) round cell infiltration. Most of these lesions disappear completely—without treatment—in a few months to a year or two. Some of them, however, develop the specific clinical features of a "determined" type of leprosy, tuberculoid, borderline or lepromatous, with the distinctive corresponding histopathological features.

If the border of the lesion becomes well-defined and papular, and pigment loss becomes more marked, then the specific accompaniments of sensory diminution within the area (preceded sometimes by recurrent or persistent paraesthesiae) indicate that cell-mediated immunity to leprosy infection will overcome the localized infection.

If, on the other hand, bacilli appear in the lesion (sometimes apparently suddenly), and similar ill-defined slightly hypopigmented lesions appear in the skin on other parts of the body, then the diagnosis is no longer "indeterminate" leprosy, but one of the "determinate" multibacillary types, that is borderline or lepromatous. And soon the distinctive clinical features of one or other of these two kinds of leprosy will become apparent.

There are some groups of people in whom special difficulty arises in the diagnosis of leprosy. These are particularly encountered in the following situations:

1. In the course of initial surveys in an area where hitherto no leprosy control programme has been in operation;
2. When fellow-villagers see the results of leprosy treatment. It is a common experience that when a leprosy treatment is working well, with competent, enthusiastic and sympathetic staff, many leprosy sufferers come out of hiding and show themselves.
3. In the course of attempts to trace the source of the infection in registered patients. The "diagnosis" of every case of leprosy should be regarded as incomplete until a real attempt has been made to answer the following questions: From whom did this patient catch the disease? and, To whom may he already have given it? Although half the patients may have no idea of the source of their infection, in villages where prevalence rates are over one per thousand, everybody must be regarded as having been exposed to the bacillus-some more, and some less.

In these three groups of people, then, there may be examples of inactive leprosy: they fall into two categories:

1. Residual lesions. These lesions are quiescent and inactive; they contain no leprosy bacilli (on standard methods of examination); and the patients do not need treatment. They should be noted, and if possible described and charted, for they provide valuable clues about the past prevalence of leprosy in the village. The best way to learn how to recognize these lesions is to follow through, over a number of years, the natural history of the skin lesions of the various types of leprosy and then to observe the residual dermal scars indicative of previous infection. Here are some of the signs in the skin:

i. Some area or areas of persistent loss of pigment. The repigmentation of the earlier lesions may be patchy, or may be more marked in the centre than at the periphery. The loss of pigment may be accompanied by any degree of scarring: its thickness will depend upon the amount of dermis involved in the original leprous granuloma.

ii. Scattered groups of pinkish papules marking the persistent border of the lesion, or part of it, the rest having completely disappeared. Sometimes the area within these papules will provide unmistakeable evidence of the previous existence of a tuberculoid lesion.

iii. An area of normally pigmented skin (that is, of repigmented skin), in which there is some fine linear wrinkling or puckering. If the latter is not immediately evident to the eye, it may be demonstrated by picking up a fold of skin between thumb and forefinger, or by pushing the skin laterally with the forefinger against resistance.

iv. Rather ill-defined areas of skin in which the surface is duller than that of the surrounding normal skin. Within these areas, there may be almost any degree of impairment of sweating, hair growth and sensation. Misreference of tactile stimuli may persist within this area and in the halo surrounding it. All these persisting changes point to a former tuberculoid lesion now quiescent.

v. Neurological deficit in the skin on the opposite side of the body, in the skin of the exact mirror image of the area when the changes enumerated in the previous paragraph have been noted. In some patients, the sensory loss in the apparently normal skin is greater than that in the area known to have been the previous seat of a tuberculoid lesion.

2. The other category of lesions often encountered in an initial leprosy survey comprises those patients with evidence of long-standing damage to the peripheral nerves. Although the skin lesions may have largely disappeared, there often remains enough scarring or hypopigmentation, or both, to suggest the identification of the form of leprosy. Very rarely—and in India more than in other countries—the trouble may be of persistent primary polyneuritic leprosy, in which there are no skin lesions, past or present .. or future. In this case, only nerve biopsy will clinch the diagnosis.

The evidence of damage to the peripheral nerves lies in the ulceration of the extremities —which is mainly the result of repeated traumata to insensitive parts; in all degrees of deformity and mutilation, depending on the actual nerve fibres damaged or destroyed; and perhaps blindness due to the sad chain of events that follows perforating ulcer of the cornea, itself the result of exposure keratitis that is the result of lagophthalmos.

While damage to the peripheral nerves is often symmetrical and late in lepromatous leprosy, it may be confined to a single main nerve trunk in tuberculoid leprosy. Moreover, while motor and sensory loss frequently occur to the same degree in the area of distribution of a main peripheral nerve, if the intraneural fibrosis is selective and partial, the result may be considerable differences in the extent of motor and sensory deficit.

In the great majority of such patients, sufficient evidence remains in the skin to permit of a diagnosis and classification being made. In India, but not apparently in Africa, leprosy may sometimes be and remain a purely neural disease; in fact, up to a sixth of newly diagnosed patients are said to have no evidence of skin disturbance, but suffer from typical damage to one or more peripheral nerves. Many of these patients, if examined thoroughly by a knowledgeable doctor or paramedical worker, will disclose residual signs in the skin. But there does remain a definite group of "primary persistent polyneuritic" leprosy. The distribution of the sensory and motor signs fits in with damage indubitably caused by leprosy. There are two ways to clinch the diagnosis, neither of them easily available: the first is to measure the nerve conduction velocity (which is typically impaired in leprous neuritis), and the second is to remove a little sliver of a cutaneous sensory nerve, and to cut sections of it and stain them appropriately. The typical histopathological picture will not only reveal the leprous origin of the damage, but will suggest the type of leprosy concerned.

With these facts in mind, and with clinical practice, the doctor or paramedical worker may with reasonable confidence approach the diagnosis of leprosy. He is wide awake, observant and suspicious, and he looks for the positive, cardinal signs of the manifestations of leprosy—

the typical picture in the skin;

the presence of acid-alcohol-fast bacilli in the skin or nasal mucosa;

the presence of signs of nerve damage in the area of skin affected, and perhaps in the corresponding nerve trunk;

the presence of the typical histopathological picture of cellular infiltration, and perhaps of leprosy bacilli in nerve tissue or in foamy cells;

the results of the lepromin test, which confirm the classification already arrived at on clinical grounds.

The diagnosis of leprosy will lose much of its mystery, and much of its terrors for the medical novice, if attention is paid to the simple advice given in this chapter.

REACTIONS IN LEPROSY

M. F. R. WATERS

Leprosy is a remarkably chronic and subdued infection. Even when leprosy bacilli are actively multiplying, their host the leprosy patient, rarely shows any significant evidence of inflammation, nor does he usually suffer from pain, fever or other systemic manifestations. Nevertheless, during the otherwise chronic course of the disease, acute or subacute episodes of inflammation commonly occur, which are the direct result of infection with *Mycobacterium leprae*, and which are not due to secondary infection or to trauma to anaesthetic areas. These episodes are traditionally known as "Reactions". Several different types of reaction are recognised, most of which have an immunological basis. However, as their mechanisms have only recently been, or are still in process of being, discovered, it is understandable that an internationally agreed terminology has not yet been developed. The names given here are those widely used in South and South-East Asia. In this region, the great majority of reactions fall into one or other of two main groups, and these will be described first.

1. Erythema Nodosum Leprosum (Lepromatous Lepra Reaction).

The name "Erythema Nodosum Leprosum" (ENL), given by the Japanese, Dr. Murata, in 1912, is used in most parts of Asia, and describes the commonest manifestation of the reaction. The alternative name, preferred in Central and South America, emphasises that ENL occurs only at the bacilliferous end of the leprosy spectrum, in lepromatous (LL), including both polar (LLP), subpolar lepromatous (LLs), and in small numbers of borderline-lepromatous (BL) patients. Although well recognised before the introduction of sulphone treatment, it is particularly common in treated lepromatous leprosy, more than 50 per cent of such patients developing ENL by the end of the first year of treatment. If LL patients are followed closely until they become smear negative, then an even higher proportion will be found to have suffered from at least one episode of ENL.

The reaction usually consists of the eruption of crops of painful, tender papules, which develop in the course of a few hours, change from bright red to purple over two or three days, and which subside over the next one to three weeks, leaving (in light-skinned patients) some residual dark discolouration of the skin, resembling bruising, which only slowly fades. The papules are particularly common along the extensor surfaces of the arms and thighs, and on the back and the face, although they may occur almost anywhere save on the hairy scalp. In dark-skinned patients, the papules may be more easily felt than seen, by running one's fingers down the back of the arms and along the front of the thighs. The papules are commonly about one to two centimetres in diameter and extend downwards to the deeper layers of the dermis, but some patients have very small, superficial papules, and others very big papules, perhaps three to four centimetres in diameter, which extend downwards into the subcutaneous fat ; occasionally papules may coalesce to form sheets or plaques of inflamed, tender skin.

Some patients may develop no more than a small number of papules, unassociated with any systemic upset, throughout the whole course of their treatment for lepromatous leprosy. Others may suffer from repeated widespread crops which continue to appear over months or years, associated almost daily with high fever (although the temperature may be normal or subnormal on waking), general malaise and headache, loss of weight, moderate anaemia, and severe aching in the limbs, either in muscle, bone or joints. In these severe cases, the ENL papules may develop into sterile pustules, or else form scabs and superficial infarcts of the skin ; in either case the lesions evolve into small but deep ulcers which on healing often leave characteristic irregular linear scars. If inadequately treated, and especially if their fever remains uncontrolled, such patients with severe ENL suffer from gross prostration and weakness, and a few may develop acute vasomotor collapse, and die. It is particularly

worth noting, that should a female patient suffering from ENL become pregnant, then she may develop an acute relapse of her reaction about a week after delivery.

Although the ENL papules are the commonest manifestation of the reaction, many other systems of the body may be involved, chiefly at those sites which harbour leprosy bacilli. Painful, tender, increased thickening of one or more of the nerves of predilection, especially of the ulnar, median or lateral popliteal nerves—ENL neuritis—may occur, and its course is usually much more protracted than that of a crop of ENL papules. If the neuritis is not energetically treated, increasing muscle weakness, or complete foot drop, may develop; therefore nerve function should be carefully monitored whenever possible by serial voluntary muscle testing (VMTs). Episodes of skin ENL are often associated with enlargement of the lymph nodes (lymphadenopathy): sometimes the enlarged nodes are painless, sometimes painful, and rarely, in severe cases, the enlarged lymph nodes may liquify and become tender chronic abcesses or cysts of sterile pus and fragmented leprosy bacilli.

Less commonly one or both eyes may become painful and inflamed from ENL iridocyclitis, or one or both testes may become enlarged and very tender from ENL orchitis—both conditions require urgent treatment to prevent blindness or infertility, respectively. Joints may also, if rarely, become swollen and tender ; in some patients it is principally the small joints of the hand that are affected, in others the large joints especially the knees and/or the ankles.

Most patients with active ENL have a polymorphonuclear leucocytosis. Many also show transient albuminuria, and on microscopy of their urine, red cells and casts may be found. In a small proportion of the latter, especially those whose ENL and lepromatous leprosy are inadequately treated by modern standards, the albuminuria becomes persistent ; subsequently they may develop signs of the nephrotic syndrome due to renal amyloidosis, and eventually die from renal failure.

Histologically, an ENL skin papule shows a number of striking features. First, there is a background of LL or BL leprosy, usually inactive or resolving under treatment, and always present even when ENL papules develop in clinically normal skin. Second, there is an intense polymorphonuclear neutrophil infiltrate, although as the lesion ages, significant numbers of lymphocytes may appear. Third, fragmented (presumed dead) leprosy bacilli are present. Fourth, inflammation of small blood vessels (vasculitis) may be found. Similar histological features are present in ENL neuritis. In ENL arthritis, synovial fluid obtained from an involved joint contains degenerating polymorphs and fragmented leprosy bacilli. However, biopsy of the kidney from a patient suffering from significant persistent albuminuria may reveal immune-complex type glomerulonephritis and/or renal amyloidosis.

Although ENL may occur in untreated patients, the episodes most commonly commence during the second six months on treatment with dapsone, or a few weeks after the beginning of rifampicin treatment. Episodes of ENL may continue for many years, but provided effective anti-leprosy treatment is continued uninterrupted, they will eventually die out when most of the dead leprosy bacilli have been removed by the body defences, i.e. when the smear bacterial index has fallen towards or to zero.

Thus ENL is important both because it is common, and because it may result in a lepromatous patient, while on correct, effective anti-leprosy treatment, suffering from chronic episodes of fever and general malaise, being unable to work, and also perhaps developing increasing nerve damage, blindness, infertility or renal damage. Unless the nature of the reaction is explained, and unless effective anti-ENL treatment is given, the chronic ENL patient may lose faith both in his medical and paramedical advisers and in his anti-leprosy (especially dapsone) treatment. As a result, he fails to take his dapsone, and eventually relapses with active, infectious lepromatous leprosy, spreading the disease to new patients, and causing the failure of the leprosy control scheme.

2. Reversal (Upgrading) and Downgrading Reactions (Borderline and Tuberculoid Reactions or Non-lepromatous Lepra Reactions)

The second main group of reactions occur over the whole of the leprosy spectrum except at the two ends (i.e. they do *not* occur in polar lepromatous, LLp, or in polar tuberculoid, TT, leprosy). Unfortunately, there is no standardised terminology ; however, most leprologists recognise two sub-groups, namely

"Reversal" or "Upgrading" in patients receiving effective anti-leprosy treatment, and "Downgrading" reactions in untreated patients.

(a) **Downgrading Reactions**

A patient with untreated low-resistant tuberculoid or borderline (that is borderline-tuberculoid, BT ; borderline, BB ; or borderline-lepromatous, BL) leprosy, may deteriorate in two ways : either by the appearance of new lesions associated with spread of the leprous granuloma without change in his leprosy classification, or by the appearance of new lesions (and the spread of old lesions) associated with a change in classification towards the lepromatous end of the spectrum. In the latter case the skin lesions (both old and new) may become erythematous and oedematous (although otherwise the lesions are in keeping with the type of leprosy the patient has or is developing) and remain so for weeks or months. This situation is known as a Downgrading Reaction.

Downgrading reactions are difficult to study for obvious ethical reasons. They are usually not severe, only involve skin and nerves, and normally settle within two to six weeks after commencing anti-leprosy treatment. Some workers even deny the existence of downgrading reactions, considering them to be the normal tissue response to rapidly spreading and multiplying *Myco. leprae*. However, at least one downgrading reaction has been carefully observed in a patient under investigation for suspected thiambutosine resistance. The patient, at the time of his reaction was BB/BL ; the reaction lasted for about three months and after it had spontaneously settled he began to develop a number of lepromatous (LLs) papules. His treatment was then changed from thiambutosine to dapsone (i.e. from ineffective to effective chemotherapy), and a few weeks later he went into a Reversal Reaction, which in appearance was very similar to, but possibly more severe than, his downgrading reaction and clinically and histologically he reverted to BL.

(b) **Reversal Reactions**

These are the important reactions occurring in treated non-lepromatous leprosy. The leprous lesions themselves become markedly swollen and inflamed, and similar new lesions may appear. The reaction develops over days or weeks, and lasts for weeks or months before slowly subsiding. The time scale is therefore very different from that of a crop of ENL papules. Many patients remain afebrile throughout their reaction. A minority develop mild fever and slight general malaise, sometimes associated with oedema of the hands and/or ankles. Marked fever and malaise is rare in Asia. Clinically and histologically the erythematous lesions are consistent with the type of leprosy the patient is suffering from or developing ; there is oedema and hyperaemia, but no extraneous infiltrate. However, as patients undergoing reversal reactions tend to shift towards the tuberculoid end of the spectrum, there may be some influx of lymphocytes, the bacterial host cells may become more epithelioid in appearance and the number of leprosy bacilli progressively diminishes.

In BT and BB leprosy, the reaction may commence within as little as two weeks from the start of dapsone therapy, and almost all within six months if treatment is taken regularly. In BL leprosy, reversal reactions frequently develop between two and 12 months after commencing therapy. By one year, as many as one third, and by four years almost a half, of all BL patients have undergone reaction, although late reactions are usually mild. BL patients may switch as far as BT, but some only upgrade to BB or BB/BL, and in some the reaction fades without any significant change in classification. Reactions are also very common in BB and common in BT leprosy ; they do occasionally occur in LLs leprosy, but such patients seldom shift beyond BL.

In severe BL and in many BB and BT reactions, the skin over the lesions becomes very dry, scaly and friable, so that the slightest trauma can cause extensive superficial ulceration. If the ulcerated lesion is on an exposed part, and especially if it is on the face, it may lead to unsightly scarring.

The other important complication is neuritis, which may occur in any nerve of predilection, but especially in those ulnar, median and lateral popliteal nerves which were thickened before the reaction commenced. Facial nerve palsy (usually incomplete) is common in patients who have a large borderline lesion on the face, involving particularly those branches of the nerve situated in or near the reacting lesion. Patients in reversal reaction should be carefully watched for the development of nerve pain and tenderness as this may signal the

onset of rapidly progressive nerve damage should anti-reaction treatment (particularly steroids) be withheld.

Any patient whose lesions are already erythematous (possibly due to mild downgrading reactions) or who has thickened, tender nerves at the time of his diagnosis, should be most carefully observed throughout the first few weeks of dapsone treatment, so that should a reversal reaction develop, prompt treatment may be given to prevent nerve damage.

The diagnosis of a reversal reaction is usually simple. However, confusion may rarely occur in LLs or BL patients, should numerous ENL papules develop in succulent annular lesions or plaques. The patient should be observed over 48 hours ; during this time ENL papules will change in appearance whereas reversal reaction lesions will remain unchanged. Correct diagnosis is important, as it will affect the management of the reaction ; in particular, thalidomide is useless in treating reversal reactions, but is as effective as steroids in the treatment of ENL.

Occasionally, the lesions in untreated polar tuberculoid (TT) patients may also become inflamed ; such patients show a natural tendency to heal (with or without treatment), and their reactions are probably akin to reversal reactions.

3. The Lucio Phenomenon

This type of reaction is included for the sake of completeness, as it has only been reported from the Americas, principally from Mexico. The Lucio phenomenon occurs exclusively in patients suffering from pure, diffuse, polar lepromatous (LLp) leprosy, without nodular lesions and with loss of the eyebrows. Such patients may develop crops of irregular, star-shaped scabs and ulcers, due to superficial infarctions (death) of the skin from severe vasculitis (inflammation) of the dermal vessels. Usually the reaction develops before the start of treatment, and subsides once the patient has settled down on effective anti-leprosy therapy. The Mexican workers are convinced that it is different from severe, ulcerating ENL.

4. Exacerbation Nodule; and Histoid Lesions

It is doubtful if relapse lesions should be classified as reactions ; however, they are important in the differential diagnosis of ENL.

When lepromatous patients relapse, whether from the development of drug resistance or from failure to persevere in anti-leprosy treatment, they may do so in a number of different ways. In many patients the relapse is relatively acute ; such patients develop over the course of days or weeks a number of erythematous, often histoid, papules and nodules, which are frequently confused with ENL. However, such lesions change little in appearance over the course of a week, are usually very asymmetrical in distribution, and are often found in somewhat unusual sites for ENL, such as the abdominal wall, flanks and buttocks. Smears taken from these new lesions have a very high bacterial index and a high morphological index ; the consistency and texture of the papule at the time of smearing or of biopsy much more closely resembles that of untreated lepromatous infiltrate than that of ENL. Moreover, the lesions are neither tender nor painful, nor is their appearance associated with systemic upset. The histology of the papules is that of hyperactive or histoid lepromatous leprosy.

If there is any doubt of the clinical diagnosis, then all that is necessary is to observe the lesions for three days, during which time ENL papules (but not relapse papules) will change in appearance ; the diagnosis can then be confirmed by the smear results. However, special care must be taken over ENL patients who relapse through ceasing to take dapsone ; such patients may develop relapse papules while still suffering from ENL, and a number of individual papules need to be smeared and observed if the dual diagnosis is to be correctly made.

COMPLICATIONS OF LEPROSY

A. B. A. KARAT

Until relatively recently, leprosy has been considered to be primarily an incurable, highly infectious skin disease associated with a variable degree of peripheral nerve damage and hence was treated in splendid isolation in leprosy sanatoria without the camp! The introduction of sulphones as specific antileprosy therapy in the mid-forties changed the entire outlook for leprosy. A fresh interest was kindled among clinicians and research workers which directly led on to the entry of leprosy into the citadels of medical establishment as a "respectable" speciality. As an inevitable consequence of this new development, leprosy entered the main stream of medical thinking and the new techniques and tools of research began to be harnessed to elucidate the pathogenesis, clinical manifestations, complications, epidemiology and prevention of this hitherto dreaded and somewhat mysterious disease. Thus we now look upon leprosy as a systemic disease with protean clinical manifestations of multiple organ involvement.

This paper, hopefully, will provide a "thumbnail sketch" of the various complications of leprosy.

Skin : The main complications in the skin are depigmentation and ulceration. The majority of skin lesions in leprosy are characterised by hypopigmentation. Ulcers appear either because of co-existent anaesthesia in these skin lesions, which results in recurrent unappreciated trauma or ulcers could result from lepromatous reactions, such as necrotising erythema nodosum leprosum. Sclerodermatous changes in the dorsum of the hands and feet is also seen in chronic E.N.L. reaction.

Peripheral Nerves : The next major consistent target for leprous infection is the peripheral nerves, in particular the ulnar, median, radial, lateral popliteal and facial nerves. The involvement of the ulnar and median nerves in the upper limbs produces the characteristic wasting of the small muscles of the hand as well as the deformity of the hand. In the majority of cases, these hands are also anaesthetic and are, therefore, frequent sites for the occurrence of trophic ulceration, chronic infection and consequent loss of digits. It must be emphasised that the mythological concept of "absorption" of the fingers due to leprosy itself needs to be refuted since leprous dactylitis by itself does not produce the deformity that one associates with leprosy. These deformities are a direct result of recurrent trauma to anaesthetic fingers which result in ulceration, sepsis and absorption of the fingers as a consequence.

Involvement of lateral popliteal nerve in the lower limb produces the characteristic foot drop deformity. In a large proportion of patients, even in the absence of foot drop, there is loss of pain and touch sensation in both the feet and this again leads to trophic ulceration, sepsis, osteomyelitis of the small bones of the feet and subsequent deformity.

Involvement of the facial nerve results in the typical deformity of lagophthalmos. The majority of these patients are not only unable to close their eyes, but have in addition loss of sensation in the cornea and conjunctivae. As a result, they develop exposure keratitis which if not treated vigilantly leads on to blindness.

A fair proportion of leprosy patients develop "glove and stocking anaesthesia" because of involvement of the fine nerve endings in the skin in the hands and feet. In some ways, they resemble the anaesthesia that one sees in such conditions as diabetes and have, therefore, the same hazards of the occurrence of trophic ulceration and subsequent deformity of the limbs.

The important message in all these neurological complications is the recognition of the role of loss of appreciation of pain and temperature in the production of deformities of the hands and feet which can progress to such a degree as to render the patient

incapable of looking after himself. In addition to the availability of surgical correction for the paralytic deformities in the hands, health education of the patient is essential if one is to save those hands and feet from the progressive destruction that occurs as a consequence of recurrent minor trauma. With the advent of elegant surgical procedures, emphasis has tended to shift from education to surgery. The patients who have had tendon transplants and re-constructive surgery for the hands and feet will not have those hands and feet for very long unless at the same time, the patient learns to protect these hands and feet from trauma that these limbs are liable to, in the carrying out of every day activities of living.

Muscle: The commonest muscle complication in leprosy is motor paralysis which is a result of peripheral neuropathy. This has already been discussed.

"Leprous myositis" is a relatively uncommon clinical manifestation of multi-bacillary types of leprosy, usually associated with erythema nodosum leprosum. Tender nodules, diffuse tenderness in the affected muscle associated with a significant rise in the serum levels of muscle enzymes characterise this condition.

Histologically demonstrable specific lesions in muscles is much more common in the dartos muscle in the scrotum. In the latter, *M. leprae* remain viable for many years after they have ceased to be viable in the skin following specific antileprosy therapy. Such persisters among *M. leprae* may be important in the occurrence of relapse and in the emergence of resistant strains.

Sweating : Loss of sweating is another important complication of leprosy. The anaesthetic skin lesions are invariably anhydrotic and a proportion of non-anaesthetic skin lesions are also anhydrotic. In lepromatous leprosy patients there is widespread impairment and/or loss of sweating over the trunk and limbs, often in a patchy manner probably due to destruction of sweat glands and/or destruction of nerve supply to the sweat glands by the lepromatous process. It becomes clinically important in the tropics where such patients are unable to adequately regulate their body temperature in the hot weather. Loss of sweating in the limbs, especially the hands and feet, also leads to dry, scaly skin with a tendency to development of "dermatitis", deep fissures in the palms and soles of the feet which also predispose to ulceration.

Reactions : Reactions in leprosy represent an exacerbated state of the disease due to altered immune mechanisms. They could be broadly considered according to the type of leprosy, whether multi-bacillated (borderline and lepromatous) or pauci-bacillated (tuberculoid). So far, no-one has been able to substantiate the occurrence of "reactions" in the so-called indeterminate type of leprosy. Reactions in tuberculoid leprosy are essentially characterised by the occurrence of acute neuritis, involving one of the peripheral nerves, in particular the ulnar nerve, median nerve, lateral popliteal nerve and facial nerve, characterised by intense pain along the affected nerve with associated sensory and/or motor loss in the territory of supply of that nerve. These episodes of exacerbation may occur without warning quite suddenly, especially when the patient is on specific antileprosy treatment and may produce catastrophic neurological deficits within a matter of two to three days. With the currently available lines of treatment with anti-inflammatory drugs, these reactions need no longer be a major threat to the integrity of peripheral nerves, provided they are anticipated and treated vigorously at the very onset.

Reactions in bacillated types of leprosy : There are a number of clinical manifestations of reactions in bacillated types of leprosy, of which erythema nodosum leprosum (E.N.L. reaction) is the most common and most typical. This is characterised by the appearance of tender, erythematous nodules over the limbs and trunk associated with general ill health, a rise in temperature, swelling of the feet, pain along the peripheral nerves, epididymo-orchitis, lymphadenopathy, hepatosplenomegaly and iridocyclitis, scleritis, etc. These reactions are currently believed to be mediated by immune complexes which are deposited at various sites and they tend to occur more frequently in patients on treatment than among the untreated group of patients. Until very recently, one had very few effective therapeutic measures available, other than the exhibition of cortisone with its own hazards. The introduction of Clofazimine and, strangely enough, Thalidomide, have completely changed the outlook for patients who were once subject to this distressing complication which progressively damages the organs that are affected during the course of the illness.

The other triggering mechanisms for the occurrence of reactions are childbirth, intercurrent infection especially tuberculosis.

Kidneys : So far, no-one has demonstrated direct leprosy involvement of the kidneys nor have specific leprosy lesions either lepromatous or tuberculoid been reported in the kidneys. On the other hand, in bacillated type of leprosy, particularly the lepromatous and borderline lepromatous group, *M. leprae* can be demonstrated in the urine. Bacilluria increases, for some reason, during the proteinuria. "Leprous nephritis" in its clinical, biochemical and histological features resembles post-streptococcal nephritis. It is, therefore, suggested that "leprous nephritis" is also an immune complex disease and can result in severe impairment of renal function in the affected patient.

Amyloidosis of the kidney is an additional hazard in patients with bacillated types of leprosy. It is an important cause of death among patients in leprosy santatoria round the World, more so among patients of the Caucasian race. It usually manifests itself as gross pitting oedema of the lower limbs associated with marked proteinuria. In the early stages, there is no significant change in the blood chemistry other than the appearance of hypoproteinaemia. Unfortunately, amyloidosis of the kidneys is an irreversible process and tends to gradually progress on to chronic renal failure and death.

Haematological complications : Anaemia is a very common manifestation in patients with bacillated types of leprosy and it has been demonstrated that part of this anaemia is due to the chronic infection. In others, the anaemia is due to a conditioned deficiency of folate and B.12 presumably dependent on the proliferative activity of *mycobacterium leprae*. The anaemia could also be in part due to replacement of the haemopoeitic tissue by leprous infiltration.

Liver and the reticulo-endothelial system : In the bacillated types of leprosy there is marked alteration of liver functions associated with a sharp rise in globulins, particularly the gamma fraction and a lowering of serum albumins. In one of the control trials using Clofazimine for treatment of lepromatous leprosy, it was demonstrated that with the regression of lepromatous disease, there was a significant improvement in liver functions and the reversed albumin:globulin ratio tended to become normal with no other therapeutic intervention, suggesting that in fact the original alterations in liver functions were a direct result of involvement of the liver by the leprous process. Liver function changes are relatively uncommon in the non-bacillated types of leprosy, except during reactional phases. Specific granulomata in the liver have been demonstrated in all types of leprosy, except indeterminate leprosy.

Splenomegaly occurs in over a third of patients with active multi-bacillary forms of leprosy and tends to regress with specific anti-leprosy therapy at the same time as the disease itself. During E.N.L. reaction, 75% of patients have splenomegaly.

Lymphadenopathy is frequently seen in the bacillated types of leprosy and localised enlargement of lymph glands in the territory of the skin lesions of tuberculoid leprosy have also been noted. On biopsy, these lymph glands demonstrate the pathological features of the type of leprosy found in the individual patient.

During reactions in the bacillated types of leprosy, these lymph glands tend to become acutely inflamed and can on occasion develop "sterile abscesses" and burst, pouring blood-stained, purulent material which may mimic that seen in patients with tuberculous lymphadenitis. Both the lymphadenopathy and lymphadenitis settle down on treatment of the primary disease without the need for additional intervention with antibiotics.

Lymph glands are also of particular interest in that when the disease appears quiescent elsewhere, biopsy of these glands may demonstrate acid-fast bacilli. These "persisters" among *M. leprae* may have a major part to play in the appearance of relapses or in the emergence of resistant strains of bacilli.

Systematic examination of bone marrow aspirates from patients with various types of leprosy have demonstrated the presence of significant numbers of viable acid-fast bacilli. What is more interesting is that after several years of specific antileprosy treatment, one can still demonstrate bacilli in the bone marrow which can in a proportion of patients be shown to be viable using the mouse foot-pad inoculation technique. It is, therefore, conceivable that these persisters among the acid-fast bacilli in such sites as bone marrow, liver, lymph glands, muscles nerves, etc., may be responsible for both relapses of leprosy and the emergence of resistant strains.

Endocrines : Gynaecomastia is not an infrequent occurrence among patients with bacillated types of leprosy, particularly towards the lepromatous end of the spectrum. So far, the various attempts to elucidate the pathogenesis of gynaecomastia have failed to explain satisfactorily the precise cause of gynaecomastia in leprosy. For example, while undoubtedly lepromatous leprosy results in testicular atrophy in a large proportion of patients, there is no consistent relationship between the size of the testis, the histological appearance on testicular biopsy, the level of 17 keto-steroids in the blood and the presence or absence of gynaecomastia. As already mentioned, there is no doubt that the liver is frequently involved in patients with leprosy; however, there is no consistent relationship between the degree of hepatic dysfunction and the occurrence of gynaecomastia.

Adrenal glands are affected in about 30% of patients with bacillated types of leprosy and careful study of adrenal-pituitary functions have demonstrated changes in the adrenal function in lepromatous leprosy. Further, during reactional phases of leprosy, there is a clear deterioration in the adrenal function which tends to recover somewhat with the subsidence of the reactional episode. Postmortem studies have left no doubt of the leprous involvement of adrenal gland in a fair proportion of patients with lepromatous leprosy. As yet, adrenal involvement with patients with non-bacillated types of leprosy has not been reported.

Ear, nose and throat : Involvement of the nasal mucous membrane occurs very early in patients with lepromatous leprosy and, in fact, current studies on the epidemiology of leprosy, tend to implicate the nasal mucous membrane as an important source of *M. leprae* for transmission of leprosy in the community. Patients usually present with stuffiness of the nose and/or epistaxis. When the local infiltrative process progresses, there is gradual destruction of the nasal septum (bone and cartilage) which finally produces the typical sunken nose that one associates with advanced lepromatous leprosy. The experienced clinician can distinguish this appearance from that produced by syphilitic collapse of the nose.

Perforation of the hard pallate in the mouth is another rare manifestation that occurs in severe lepromatous leprosy of long standing. Lepromatous nodules may be seen on the tongue and along the alveolar margin (personal observations) as well as in the fauces in the mouth.

Leprous involvement of the larynx was a very common complication in the pre-sulphone era, leading on to laryngeal stenosis and death unless there was prompt surgical intervention with tracheostomy. The leprous laryngitis is also a cause of recurrent haemoptysis, brassy cough and hoarseness of voice. In untreated highly bacillated lepromatous leprosy, these clinical features can be seen and recognised even today and it is gratifying to note that they tend to regress within six months to a year from intervention of specific therapy.

Involvement of the external ear in leprosy almost exclusively seen in patients at the lepromatous end of the spectrum. The major changes that one may see are gross infiltrative lesions, enlargement of the ear, nodules along the pinna and ulcerations in the ear, if the ear is involved in the E.N.L reaction. To date, involvement of the internal ear in lepromatous process has not been reported.

In the bacillated types of leprosy, there is a gradual loss of eyebrows which may in some patients progress to complete loss of eyebrows (madarosis) necessitating re-constructive plastic surgical procedures to restore cosmetic appearance.

Bones : Specific involvement of the skeleton in non-bacillated types of leprosy has not been confirmed. It is not an infrequent feature in the bacillated types of leprosy, even in radiologically normal-looking small bones in the hands and feet. Trephine biopsies have demonstrated lepromatous granuloma in patients with moderately advanced lepromatous leprosy. The frequency of occurrence of leprosy bacilli in bone marrows has already been referred to. Leprous dactylitis involving the small bones in the hands is characterised by osteoporosis and sub-cortical osteolitic lesions. In addition, quite often there is a loss of the "tufts" in the terminal phalanges in advanced lepromatous leprosy. Leprous involvement of these bones in the hands and feet render them liable to pathological fractures with significant development of bizarre deformities, most of them dependent on the occupation of the particular patient. The leprous periosteitis of the tibia is fairly common, which results in an anterior bowing of the leg and radiologically can be seen as marked thickening

of the cortex in the affected bone. The appearances superficially mimic Paget's disease.

Eyes : There is no evidence of involvement of the eyes in tuberculoid leprosy except in the rare event of direct infiltration of the tarsal plates in a patient with an active tuberculoid lesion involving the eyelids. On the other hand, facial nerve paralysis is a relatively common event in tuberculoid leprosy and the consequences of such a lesion have already been discussed under peripheral nerves.

Specific lesions of the conjunctiva, sclera, iris and external occular muscles is fairly common in multi-bacillary forms of leprosy. By and large, these specific lesions tend to be asymptomatic. However, in an as yet unpublished study, viable *M. leprae* were demonstrated in the iris in lepromatous leprosy patients who had been on specific antileprosy treatment for five or more years and had attained bacteriological negativity on repeated skin smears (personal observation).

The more sinister eye complications of leprosy occur as manifestations of "reactions" in the form of keratitis, iritis, irido-cyclitis and scleritis and result in chronic headache, photophobia, painful eyes and progressive impairment of vision. It is important to look for these eye complications since early treatment results in very satisfactory remission. Apart from local steroids during the acute phase, Lamprene is by far the most effective anti-inflammatory agent to suppress the immunologically mediated insult to the eyes.

Summary

Leprosy is essentially a systemic disease and is a great "mimicker" of many other diseases. It affects apart from skin and peripheral nerves, haemopoietic, reticulo-endothelial and endocrine systems as well as eyes, bones and muscles.

PLANTAR ULCERS

H. SRINIVASAN

1. Ulcers are found all over the body of leprosy patients and they are all due to leprosy

No, that is not true. Ulcers can occur anywhere on the body of the leprosy patient, but usually they do not. Most commonly they are found on the feet, on the undersurface i.e., the soles, and these are known as "plantar ulcers". Less often, ulcers may occur on the fingers and hands and occasionally elsewhere on the body, on places like the forearm, thighs, back or front of the trunk of the body. Ulcers occurring in places other than soles of the feet and hand are not common, and only they are due to leprosy (leprous ulcers), whereas ulcers in the soles and hands are only indirectly attributable to leprosy. Leprous ulcers are quite rare and are due to uncontrolled leprosy or they occur during acute inflammatory phases of leprosy known as "reactions". Leprous ulcers are temporary phenomena and they readily heal with anti-leprosy treatment.

2. Practically every leprosy patient will get ulcers in his feet

No. That is not true either, although it is popularly believed that every leprosy patient will get ulcers in his feet, it is not so. In fact, only 10% to 15% of leprosy patients have or have had ulcers in their feet. This means that 85% to 90% of leprosy patients do not have or have not had ulcers in their feet. This is because the ulcers occurring in the soles of feet (plantar ulcers) develop only under certain specific conditions, which are found only in about 20% of leprosy patients. That is the reason why the great majority of leprosy patients do not suffer from and are not likely to develop ulcers in their feet.

3. All persons with chronic ulcers in their feet are leprosy patients.

No. That is also not correct. There are a number of other conditions in which identical ulcers indistinguishable from those seen in leprosy patients occur. For example, Diabetic neuropathy (degeneration of peripheral nerves occurring in diabetic patients), Syphilis of the nervous system (neurosyphilis), Spina bifida (a congenital malformation of the spinal cord), and Paraplegia (paralysis of both lower limbs usually due to injury to spinal cord) are some of the conditions in which the patient may develop ulcers exactly like those seen in leprosy patients. Therefore, just by the presence of an ulcer in his foot or by the look of it we cannot say that the person has got leprosy. But, in areas where leprosy is very common, leprosy patients with such ulcers are more commonly seen than others. That is natural, because the other conditions are not so common as leprosy.

4. Are plantar ulcers not due to leprosy? Why then are they seen in leprosy patients?

Instead of giving a straight Yes or No answer to this question it will be more informative if we trace our ideas of causation of plantar ulcers in leprosy patients.

It used to be thought, till the later part of the last century, that leprosy was directly responsible for plantar ulceration. It was generally assumed that leprosy somehow devitalized tissues which "rotted and dropped off" and that when bone tissue was thus devitalized by leprosy it died and the tissues ulcerated to get rid of the dead bones. This belief was fostered because, when the dead bone was removed from the depths of these ulcers, they healed, or, contrarily, the ulcer did not heal until the dead bone was removed. We now know that leprosy does not lead to devitalization or death of bones, and death of bone tissue when it occurs is secondary to ulceration and infection and not other way round.

During the last quarter of last century there were tremendous advances in our understanding of the nervous system which was

disovered to control or influence the activities of nearly all organs. It was also found that many people with disorders of nervous system developed chronic ulcers in their feet. It was therefore postulated that there were a special set of nerves responsible for maintaining the integrity of cells and tissues and those hypothetical nerves were named as Trophic Nerves. It was presumed that damage to the trophic nerves devitalized the tissues, leading to their breakdown under conditions of stress and the ulcers were therefore called "trophic ulcers", a name which persists till today. The nonhealing of these ulcers was attributed to their deprivation of trophic nerves.

The theory of Trophic nerves was given up in the early parts of this century, for, assiduous search by a number of workers failed to reveal any such nerves. And so the theory of devitalization of tissues because of damage to "trophic nerves" had to be discarded. Because ulceration occurred in patients with damage to the nervous system resulting in insensitivity of their feet it was suggested that ulceration was the result of neglect of known or unknown injuries to the insensitive feet. It was argued that the patients were not aware of an injury when it occurred and, even when they knew about it, they did not bother to treat it properly, but allowed it to fester and develop into an ulcer because they did not feel any pain. In other words the ulcers were considered merely as infected and neglected wounds occurring in anaesthetic feet. This was the situation till about the middle of this century.

It was then realized that although some ulcers developed in this manner, that would not explain many others which arose spontaneously and were associated with necrosis of deep tissues. Further, the ulcers were found only in the areas of weight-bearing, at pressure points such as under the heads of metatarsal bones in the forepart of the foot and under the heel bone. It was therefore suggested that plantar ulcers were pressure sores, somewhat similar to the bed sores seen in debilitated and bed-ridden people. The hypothesis was that patients with damaged nerves and insensitivity of the soles of their feet stood for a long time in the same posture, which is not normally done because of the discomfort it causes, and subjected the weight-bearing areas to continuous unrelieved high pressures. In such a case these parts will suffer from ischaemia. Circulation of blood will be arrested in these parts due to high pressure from without, and cause death of tissues and ulceration.

In the late '50s and early '60s our concepts changed radically as the result of investigations conducted by Dr E. W. Price, then at Nigeria. He pointed out that majority of ulcers started as blisters, indicating internal damage to tissues as the initial event before ulceration. He also pointed out that most of these ulcers were seen in the forepart of the foot, nearly 75% of ulcers occurring in this part, in contrast to the heel where only about 10% of the ulcers occurred (Fig. 1). This was a clear indication that injuries (which were chance events and so would not favour one part of the sole more than any other part) and standing pressures (which are distributed evenly

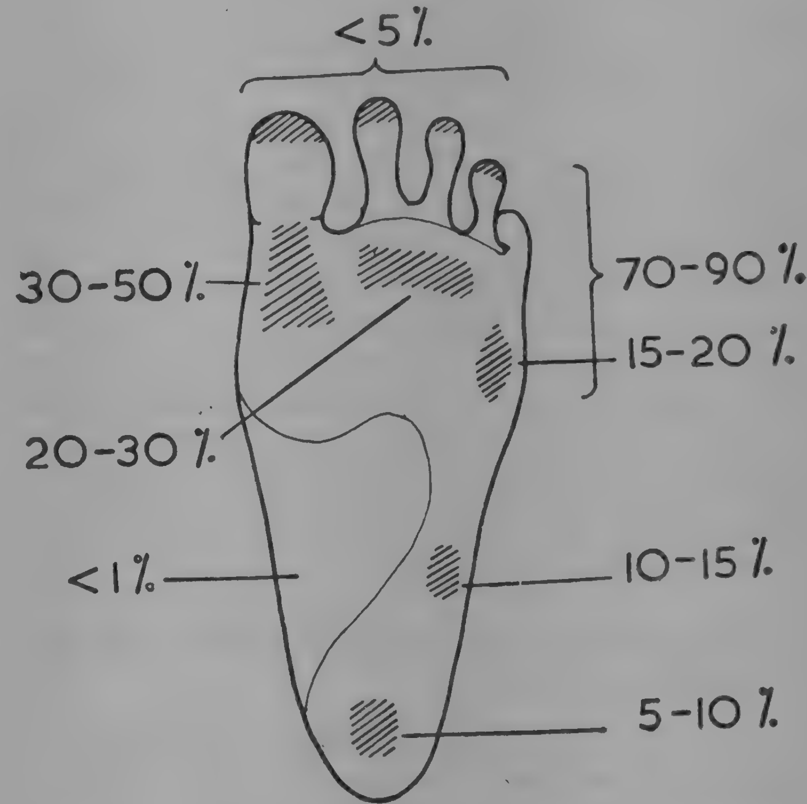


Fig. 1 Shows the proportions of ulcers occurring in the different parts of the sole of the foot.

between the heel and the forepart of the foot and not concentrated in the fore-foot) could not have been the causes of ulceration in most cases. Evidently the fore-foot is a favoured site for ulceration and the cause of ulceration must therefore be related to some special stress or strain to which the forefoot is uniquely subjected. This happens during walking. The findings of Price have been confirmed and amplified by other workers and it is now believed that plantar ulcers occur because of three reasons (i) Injury from outside, (ii) Infection of deep cracks in the dry skin of the sole of the foot and (iii) Stresses and strains related to walking. Of these three

causes, the first two account for about 15% to 20% of ulcers and the remaining 80% to 85% of ulcers (true plantar ulcers) result from the stresses and strains associated with walking.

5. But why should walking produce ulceration in the feet of leprosy patients?

Irrespective of whether it is leprosy or any other neurological disorder, the following conditions have to be fulfilled for the patient to develop ulcers because of walking. They are: (i) the foot is weakened, (ii) the patient is unable to appreciate when his foot is getting damaged and (iii) the patient uses such an unprotected and weakened foot as if it were normal, and continues to walk about without any special protective measures. Let us see how these three conditions contribute to ulceration.

(i) *Weakening of foot:* In order to understand how weakening of foot constributes to ulceration caused by walking we have to understand what happens to the foot when we walk, that is, to what stresses and strains the foot is subjected during walking.

Walking is an activity which results in forward progression of the body. The body moves forward by pushing the ground backwards by the feet. A person with only one leg can move forwards only by hopping, that is, by throwing the body upwards and forwards (by pushing the ground downwards and backwards) and as it comes down arresting its descent and again pushing it up and throwing it forwards and repeating this again and again. This jerky way of forward movement is made smoother by walking, using two feet alternately and rhythmically to propel the body forwards, but the essential shifts in the body seen in hopping are found in walking also. Thus during walking also the body is lifted upwards as it moves forwards, it then descends and the fall is arrested and the body is once again pushed upwards and forwards and this process continues. In other words, walking is a mode of moving forwards by repeated falling. Anybody who has seen the head, of a person walking on the other side of a wall, bobbing up and down can easily appreciate this fact.

During walking the two feet are in contact with the ground for a short time alternately and each foot bears the load of the body during that phase of walking, while during the next phase it is off the ground as it swings forwards and then it contacts the ground again in order to relieve the other foot of weight bearing which now swings forwards in its turn (Fig. 2). The first phase of load bearing is known as the "stance phase" and the second phase as the "swing phase". Evidently the foot cannot be subject to strains during the swing phase, for, it is off the ground during this phase and so is not bearing any load. But during the stance phase when the foot is in contact with the ground it carries the load of body weight and is subjected to a variety of stresses and strains.

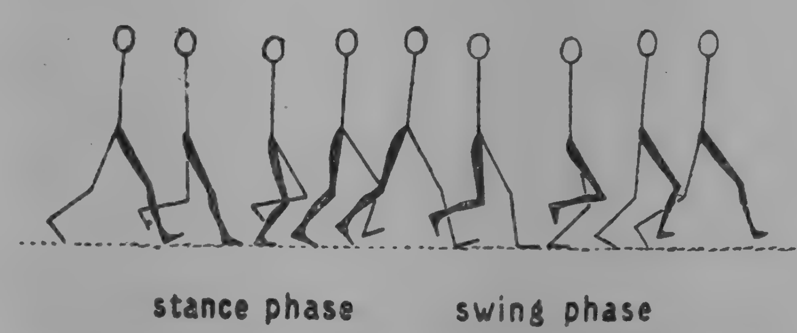


Fig. 2 Man walking (schematic) to show the stance and swing phases.

The swing phase is terminated and the stance phase commences when the heel contacts the ground to arrest the descent or fall of the body. Immediately after the heel strikes the ground the forefoot also comes down and the whole foot is then in contact with the ground (Fig. 3). The load initially borne only by the heel is now borne by the whole foot. During this time the body is also moving forwards. A fraction of a second later the heel is raised, the body load is shifted upwards and forwards and only the fore-foot now bears the load. At this moment the fore-foot pushes the ground backwards for further forward movement of the body. As the body moves forward for some more distance, the perpendicular through the centre of gravity of the body falls beyond the base of support and the body starts falling, i.e.,

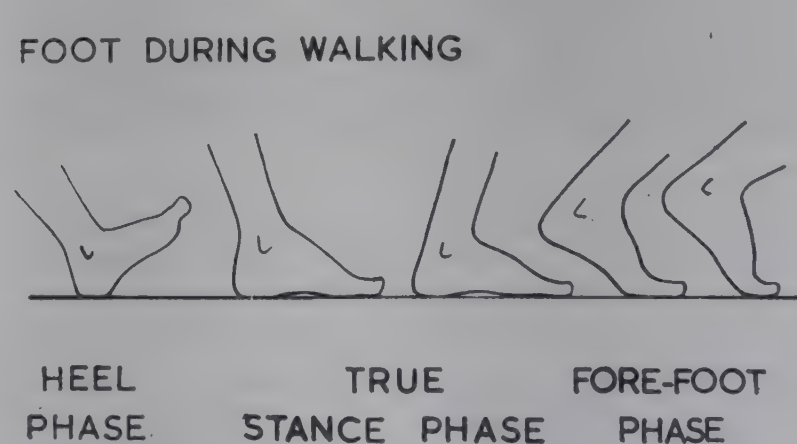


Fig. 3 The foot during the stance phase.

descends under the influence of gravity. During this "push-off" stage of walking the forepart of the foot is deformed and is also subjected to compression, bending, distraction or tension and shearing forces. There are a number of small muscles in the foot which normally come into activity precisely during this stage of walking and their contraction tends to counter and reduce all the above mentioned forces (Fig. 4). In many leprosy patients, and others with damage to the nervous system, these muscles are weakened or paralysed and the fore-foot is then deprived of their protective action and the walking strains are unchecked. In course of time the tissues in the forepart of the foot are unable to bear the increased strain and they break-down, the exact site of breakdown depending on many other factors like the gait, minor anatomical features etc.

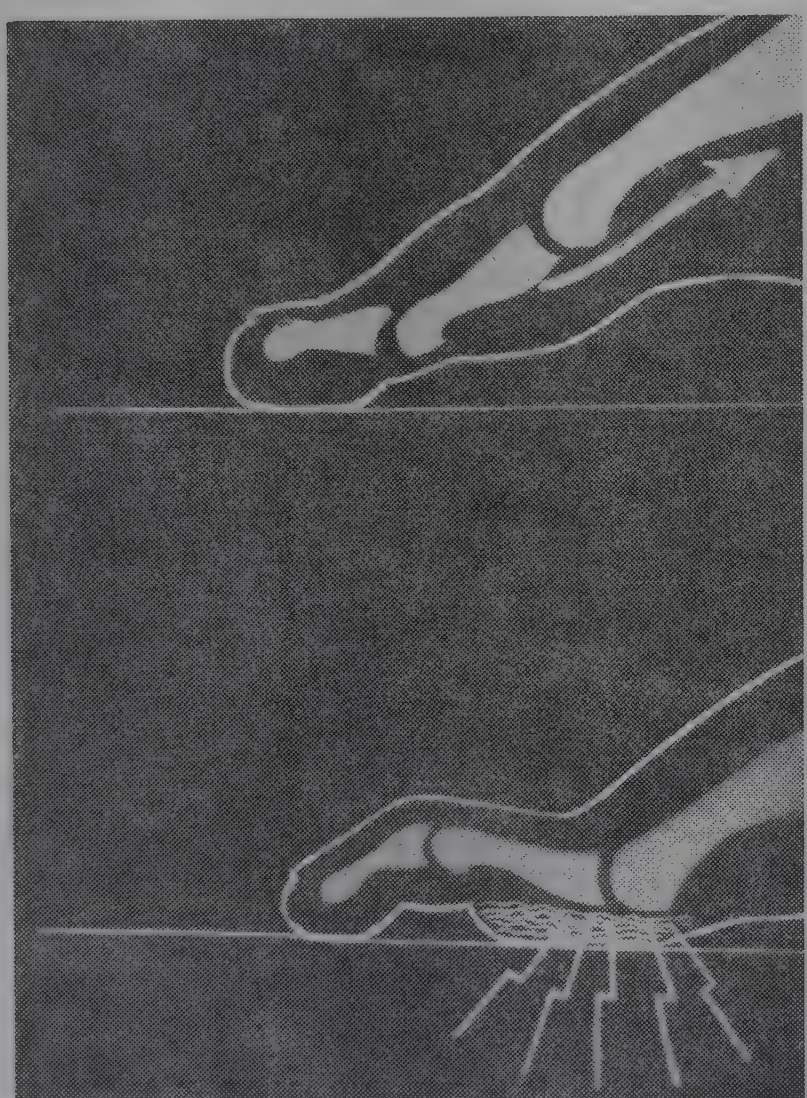


Fig. 4 Shows the effect of functioning intrinsic muscles of the foot (above) and the consequence of their paralysis (below).

(ii) *Lack of protection because of anaesthesia:* When such a weakened foot is also insensitive, the person does not know that the tissues of his foot are damaged. Ordinarily we become aware of any damage to our tissues because we feel pain in the part. A person with insensitive foot does not feel any pain and so is not aware when it gets damaged and the patient is thus deprived of the natural protective mechanism of pain. In leprosy the posterior tibial nerve behind the ankle which supplies the small muscles and serves the skin of the sole of the foot is very frequently infected with *M. leprae* and in about 20% of patients this nerve is damaged sufficiently to produce paralysis of the small muscles of the foot and insensitivity of the plantar skin.

(iii) *Continued walking:* Such a foot, though it is "substandard" because of paralysis and anaesthesia, does not appear particularly abnormal and the patient does not experience much difficulty in using it, although some find it rather strange not to feel the ground properly under their feet. Thus we have the vicious combination of circumstances that ultimately lead to ulceration.

6. So, will only leprosy patients with anaestheic foot develop ulcers?

Anaesthesia (or loss of sensation) of the sole of the foot is the first pre-requisite for ulceration. As mentioned earlier, such feet can be injured without the person being aware of it. But the patient with mere anaesthesia of the sole without any paralysis of the small muscles of the foot can get ulcers only from infection of wounds or cracks, and not from walking. But if he also has paralysis of these muscles his chances of developing ulceration increase very much and unless he takes precautionary measures he is bound to get his foot ulcerated sooner or later, because of walking.

7. What happens actually which ends as ulceration?

In the early stages when the strains are increased to some extent the tissues are able to bear it. But continuously repeated excessive strain, even if it is only mildly excessive, ultimately damages the tissues by causing haemorrhage and death of tissues possibly by blocking of fine blood vessels because of damage to the inner lining of these vessels. This sets up an area of tissue necrosis and aseptic inflammation with some swelling of the tissues. This is the stage of threatened ulcer.

If the patient continues to walk about, more tissue is damaged and autolytic enzymes

digest the damaged cells and tissues and liquify them so that there is a collection of blood stained fluid in the area. The fluid is forced to come to the surface due to pressure and it appears as a blister. This is known as "necrosis blister". This is the stage of concealed ulceration, because the essential process of ulceration has already taken place, this being destruction of the tissues.

The next stage is the stage of open ulceration. The blister breaks open either from a trivial injury or because the skin gives way. Then the sore is there for all the world to see (Fig. 5).

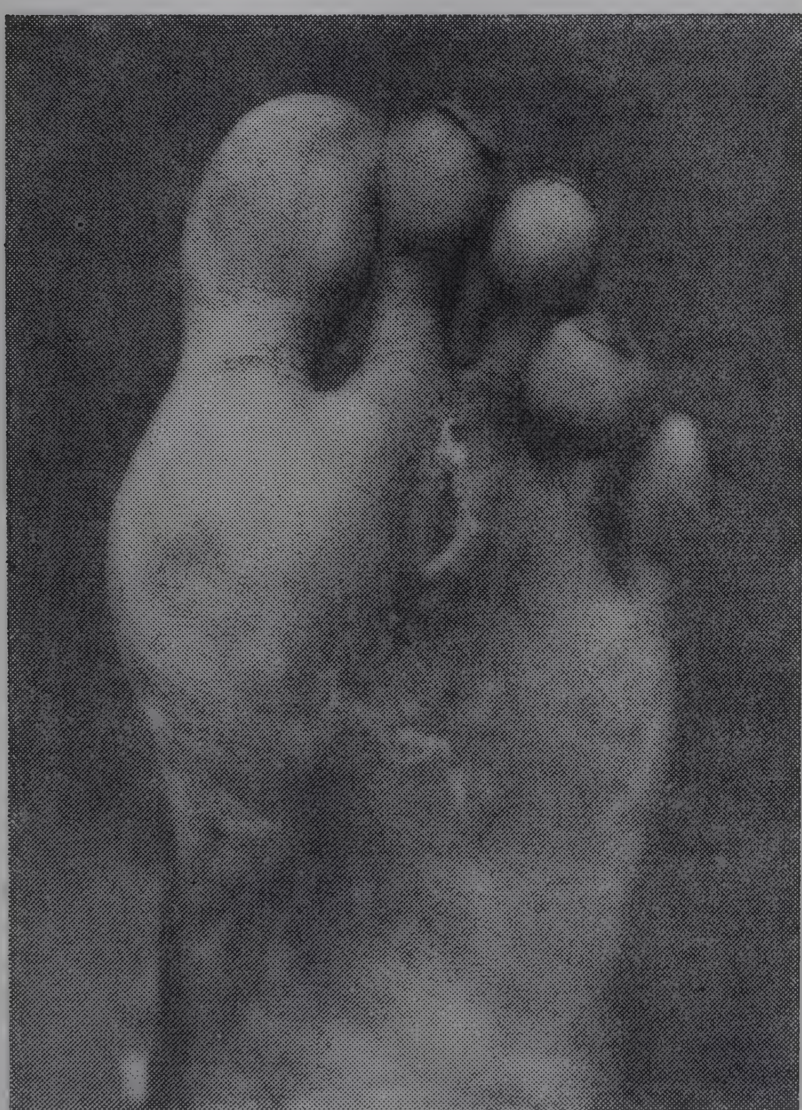


Fig. 5 A small hlantar ulcer.

8. What will happen if we leave the ulcer alone?

If the ulcer is ignored it gradually extends in size and depth as more and more tissue is destroyed by walking (Fig. 6). Foot not being a very clean place, the ulcer will inevitably get infected with pyogenic organisms like staphylococci, streptococci and B. Coli and is converted into a frankly septic wound. The foot gets swollen and painful and the ulcer copiously discharges foul smelling pus. More tissue gets destroyed in the process, and infection reaches the underlying structures like the bone, joint or tendon sheath.

Fig. 6 Large ulcer. Some toes have already been lost.

At this stage the patient usually seeks treatment and the ulcer may heal leaving an unstable scar or it may become quiescent once more. The patient continues to walk and if previously healed, the scar breaks down and the ulcer occurs once again and in course of time gets acutely inflammed again with further damage to the deeper tissues. This cycle (of ulceration—acute inflammation—healing —ulceration) is repeated a number of times and ultimately that part of the foot is more or less completely destroyed. Thus the toes may get deformed and the foot is foreshortened and mutilated (Fig. 7).

Or, if the ulceration has involved an unfavourable site like the middle of the foot or the heel, the infection extends deep into the foot, to involve the major tarsal bones of the foot, like the cuboid, calcaneum or talus and this leads to a major break-down of the foot (Fig. 8). Sometimes infection can extend along tendon sheaths to joints like the ankle joint or up into leg, to the calf region, giving

rise to septic arthritis and widespread destruction of tissues. Such extensive infection can become uncontrollable and the foot may have to be amputated to prevent further spread. Patients with chronic dirty ulcers in their feet can get lethal infection like tetanus or gas gangrene which can endanger their lives. Occasionally even malignant growths can develop from the chronic ulcers (Fig. 9). Therefore it is essential that the ulcer is healed as early as is possible and measures are taken to ensure that it remains healed.

Fig. 7 Late effect of repeated ulceration.

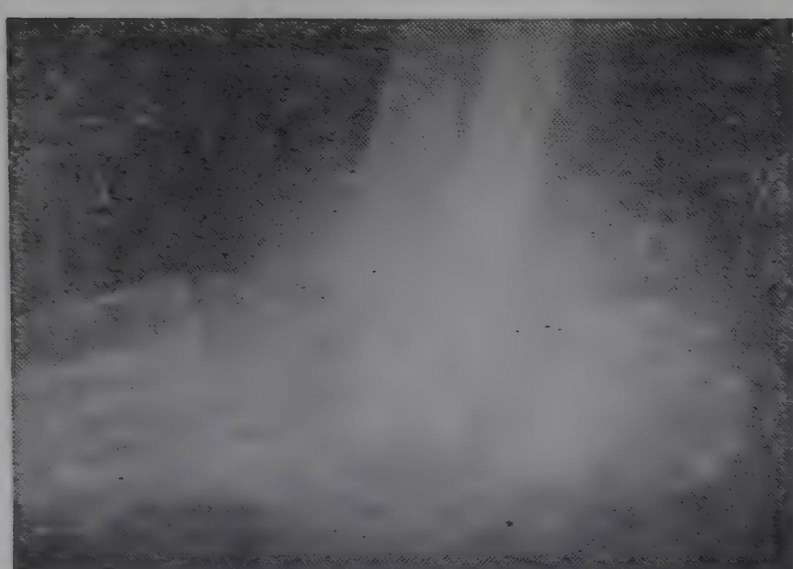


Fig. 8 X-ray showing complete disorganization of the skeleton of the foot due to spread of infection.

Fig. 9 A malignant growth arising from long standing plantar ulcer.

9. Are these ulcers curable?

Plantar ulcers are definitely curable because there is nothing wrong with the healing processes of the tissues, even in leprosy patients. But, for the ulcers to heal they must be treated. The plantar ulcers do not heal in most patients because they are not treated and not for any other reason. It must be realized that treatment does not mean mere applying of some medicine over the ulcer and wrapping it with a piece of cloth or bandage. If the ulcer is treated properly it will heal (Fig. 10) and if proper precautions are taken it will remain healed.

10. What should be done to heal the ulcers?

Treatment of the ulcer depends on the condition of ulcer. From this point of view the ulcers may be broadly classified as (a) acute ulcers, (b) chronic ulcers, (c) complicated

ulcers and (d) frequently recurrent ulcer, because for each type the treatment will have to be different.

Fig. 10 a A large plantar ulcer.

In *acute ulcers,* that is acutely inflamed ulcers, the patient must be put to bed, and prohibited from walking. The foot should be kept elevated and the profusely discharging ulcer must be dressed frequently using sterile dressings and aseptic dressing technique. Local use of antibiotic creams is not advisable and gauze soaked in freshly prepared EUSOL (12.5 G of Boric acid and 12.5 G bleaching powder dissolved in one litre of water) is the best for dressing. If need be the foot should be soaked in the antiseptic solution and the ulcer irrigated with the same. If there is any collection of pus, it must be drained out. If the patient is toxaemic, with fever etc., suitable antibiotics must be given. Otherwise antibiotics are not necessary. Under this line of treatment the acute inflammation subsides in a few days and the acute ulcer is converted into a healing ulcer. If infection of bone or joint is suspected the foot should be X-rayed and the condition treated accordingly. Otherwise the ulcer is treated from then on like a chronic ulcer.

The *chronic ulcer* remains indolent because it is not allowed to heal or because of some complication. If there are no complicating factors, like infection of underlying bones or joints, we can presume that the ulcer did not heal because it was not permitted to heal. When a person of average weight of 60 Kg. is standing, each foot bears half the body weight (30 Kg.), but when a person is walking this load increases and it may even exceed the body weight. This is more so during running, jumping and such activities. If the ulcer is repeatedly subjected to such loads and other strains mentioned earlier, the delicate granulation tissue and epithelium which have to grow, fill and cover the ulcer are damaged and healing is actively prevented. The ulcer thus remains chronic.

Fig. 10 b The same healed after routine treatment.

Therefore if the ulcer has to heal it must be protected from excessive loading and the other strains generated by walking. This is best achieved by encasing the foot and leg in a plaster of paris cast (Fig. 11). The patient

can walk with the plaster cast, for, the cast protects the fore-foot from deformations and other strains and also relieves the ulcerated area from excessive loading (compression stress) by distributing the load to the entire surface of the sole of the foot. The cast is usually kept for about six weeks by which time the ulcer heals.

Fig. 11 Leg in walking plaster cf paris cast.

In case of *complicated ulcers* the particular complication which is interfering with healing must be identified and treated, using appropriate measures. Surgical treatment by exploration, removal of dead bone or other dead tissue deep inside the foot, clearing of foci of infection in the bones and deeper tissues are some of the measures that are often needed for this purpose. Afterwards the ulcer is treated like a chronic ulcer.

11. But these ulcers come up again! Why is it so?

The ulcer will recur again unless special protective measures are taken. As pointed out earlier, healing is only one stage in the natural history of plantar ulcers, the next stage being recurrence of the ulcer. It is not very difficult to see why the plantar ulcer does not remain healed, but recurs. As long as the original combination of conditions which led to ulceration (anaesthesia of the sole, paralysis of small muscles of the foot and walking) continues, it will again lead to ulceration. The only difference will be that the ulcer will come up sooner this time because the scar tissue which replaces the original fibro-fatty subcutaneous tissue of the sole of the foot is inferior in its capacity to withstand the stresses and strains like compression, bending and shear. So it breaks down sooner than the normal tissues. Further, in some patients there are associated deformities of toes or foot as the result of previous ulceration or independent of that and those deformities usually make the scar more vulnerable because they tend to increase the stresses on the scar.

12. How can we prevent the ulcer coming again?

We saw that the ulcers recurred because (a) the original causes leading to ulceration continued, (b) the scar tissue was inferior in quality and (c) associated deformities subjected the scar tissue to increased stresses. The original causes leading to ulceration are anaesthesia of the sole of the foot, paralysis of small muscles and walking. Of these, anaesthesia and paralysis are permanent and we have no way of restoring sensation or reactivating the paralysed muscles, and we cannot ask the patient to stop walking. Nevertheless, stresses and strains generated by walking can be reduced by (a) reducing walking and (b) interposition of shock-absorbing material between the ground and the foot.

Reducing walking: Although walking cannot be avoided it can be minimized and walking long distances or for long periods can be avoided by using a vehicle (even a bicycle is better than walking), or taking rest periodically so that one does not walk continuously for a long stretch of time or distance.

Running, jumping and other activities are, of course, very damaging and should be avoided as far as possible.

Use of shock-absorbing insole: Besides reducing walking, one should also see that the stresses generated by walking are reduced. This is achieved by interposing a resilient insole in the foot-wear so that the ground reaction is dampened and is felt in a reduced form by the foot. Sheets of microcellular rubber (not sponge rubber) of 10° to 15° hardness is the best for this purpose (Fig. 12). In some patients this by itself may not be sufficient and the forces at the site of ulceration will need to be further reduced by other modification in the foot-wear, like addition of metatarsal bar or moulding of the insole. Generally these modifications increase the area of load bearing and thus reduce the intensity of load at any point. In this manner, by suitable foot-wear, one can relieve the foot and the ulcer-bearing site of stress to a great extent.

Fig. 12 Microcellular rubber of 15° hardness

In certain cases skin grafting of the ulcer or surgical revision of the scar will have to be done to improve the quality of the scar. Similarly, where a deformity throws excessive strain on the scar, that should be corrected. These procedures will also help to prevent recurrent ulceration.

13. Is it not possible to prevent these ulcers in the first place?

That is certainly possible and actually that is what one should aim at, for, once an ulcer has occurred there is the ever-present danger of it occurring again. As mentioned earlier, ulcers in the foot arise from injuries, infections through cracks and walking. All measures taken for preventing recurrence of ulcer, if followed from the beginning, will also prevent the first occurrence of the plantar ulcer. In addition other measures must be taken to protect the foot from injuries and infection. Injuries can be prevented by the constant use of foot-wear with tough soles, resistent to thorns, sharp stones and short nails. It is for this reason that tyre side pieces are used as the outer sole in the foot-wear for leprosy patients (Fig. 13)—Tyre side pieces are cheap, tough and durable and protect the foot very well. Nails in the foot-wear will injure the foot and that is why it must be insisted that all fixation of straps and soles is done by stitching or with adhesives, and not by hammering in nails. (Fig. 14). Infection through cracks can be avoided by preventing fissuring or cracking of the skin. For this, the skin of the sole of the foot (which becomes dry and brittle when its nerve supply is damaged

Fig. 13 Foot-wear with microcellular rubber insole and tyre sole.

Fig. 14 Shows that the soles and straps are secured by using adhesive or by stitching. Note no nails are used.

and sweating ceases as the result) should be kept hydrated and supple. Daily soaking in water or saline for a few minutes, mopping the excess water and smearing the foot with a thin coat of oil or grease to retain the moisture will keep the skin soft and prevent its fissuring. Even when injuries have occurred or cracks have appeared, prompt and proper treatment of the same will prevent ulceration. Therefore *the patient must make it a habit to inspect his foot daily for injuries*. A little time spent daily on foot-care and some money spent occasionally on appropriate foot-wear is a good and worth while investment, for, in the long run that will save the patient from much misery and loss of time and money. Diligent foot-care and proper foot-wear are the best safeguards against disastrous crippling disorders of the insensitive feet.

DRUG RESISTANT LEPROSY

C. K. JOB

Until 1949 there was no effective drug to treat leprosy. The discovery of Diamino Diphenyl Sulphone (Dapsone) as an active antileprosy drug in the dosage of 100 mg. per day is a great landmark in the history of the disease (Lowe 1952). Even so, chemotherapy of leprosy lagged behind the chemotherapy of tuberculosis and other bacterial diseases because until the year 1960 *M. leprae* the causative organisms could not be cultured either in the test tube or in an experimental animal. Any drug that had to be tested had to be tried only in leprosy patients.

It is known that *M. leprae* that are killed by the drug remain in tissues for a long time. The organisms have a half life of about 100 days in lepromatous leprosy (Ridley 1964 ; Shepard et al 1968). Therefore, the immediate effect of the drug cannot be estimated by just assessing the bacillary population. Recently it has been found that effective antileprosy drugs produce granulation and fragmentation of bacilli and these granular bacilli cannot be cultured in the footpads of mice (Shepard and McRae 1965). The efficacy of a drug therefore is assessed by determining the Morphological Index (M.I.) which is the percentage of solid or uniformly stained bacilli (Waters and Rees 1962).

There are many advantages in using Diamino Diphenyl Sulphone (D.D.S.) :

(1) It is given orally in tablet form in a dosage of 50 to 100 mg. once daily and therefore is easily administered.

(2) The complications directly related to the drug even after long periods of treatment are very few and therefore medical supervision required is minimal.

(3) The cost of the drug is only Rs. 5.00 to Rs. 10.00 per year per patient and is therefore very cheap.

(4) It is now known that within 6 months of treatment no cultivable bacilli* can be isolated from most of the lepromatous patients.

(5) Most, if not all, patients getting regular antileprosy treatment will ultimately become negative for bacilli. However, due to certain unusual features of the disease it may take more than 5 years to achieve complete negativity (Lowe 1954 ; Roy 1956).

Therefore D.D.S. resistant leprosy is a serious drawback in the management of leprosy.

D.D.S. RESISTANT LEPROSY

Clinical evidence of D.D.S. resistant leprosy was available even as early as 1953 (Wolcott and Ross 1953). The presence of resistant strains was proved beyond doubt using experimental methods only in 1964 (Pettit and Rees 1964). Since then several reports of D.D.S. resistant strain of *M. leprae* from different countries have appeared (Adams and Waters 1966 ; Rees 1967 ; Jacobson 1973 ; Taylor et al 1974).

Resistance to D.D.S. was initially suspected following repeated clinical and bacteriological examinations when no improvement was noticed despite a fairly long period of treatment. Then it was confirmed using mouse footpad culture techniques. The 4 groups of animals used for the experiment are given injections into their foot pads of 10^4 *M. leprae* isolated from the patient suspected of D.D.S. resistance. Three groups of these animals are given food pellets containing 0.01 per cent, 0.001 per cent, and 0.0001 per cent of D.D.S. respectively. The fourth group are used as control animals and are given normal diet. At the end of 6, 8 and 10 months, animals from each group are sacrificed and bacilli are harvested from the foot pads. If the organisms are found to grow in all animals given D.D.S. in food, and controls, the organisms belong to a highly resistant strain. If the organisms grow only

(* In the mouse foot-pad—Editor).

in control animals they are of a strain highly sensitive to D.D.S. If they are found to grow in control animals and in those receiving low concentrations of D.D.S. in the diet the organisms are fairly sensitive to D.D.S.

In our experience in South India with 39 patients, 6 experiments failed in that no growth was obtained in all 4 groups of mice. Fourteen were found to be highly sensitive to D.D.S. Seven were mildly sensitive to D.D.S. and 12 were resistant (Taylor et al 1974).

Waters et al (1975) have detected 98 patients from Malaysia resistant to D.D.S. using experimental methods. Clinical evidence of resistance was seen from 5 to 24 years after D.D.S. treatment. More than 2/3 of patients remained negative for many years before relapsing with D.D.S. resistant strains of bacilli. Low dosage and intermittent administration of D.D.S. favoured sulphone resistance.

In our experience 6 of the 12 from whom resistant strains were isolated had episodes of reaction and were given intermittent D.D.S. Some had low dosage of D.D.S. for varying periods. The resistant strains were isolated 4 to 30 years after commencement of treatment. It is interesting to note that there was also an instance of a patient who had D.D.S. 100 mg. regularly and remained negative for 12 years and then relapsed with organisms resistant to D.D.S.

D.D.S. resistance has also been reported from other parts of our Country (Chaudhury and Desikan 1975). There is no doubt that there are significant number of patients in different parts of our country who are D.D.S. resistant but are not detected for lack of adequate facilities. However, it must be pointed out that although D.D.S. has been in use for over 25 years the resistant strains of *M. leprae* now known in our country are a small number. The main reason may be that the dosage of D.D.S. given is 50 to 100 mg. per day which is 50 to 100 times the effective dosage against *M. leprae.*

Although primary resistance to D.D.S. is not yet reported, the possibility of emergence of it soon cannot be disputed.

It is important to treat patients with combinations of drugs to reduce incidence of drug resistance. Combined therapy in mice have been reported (Shepard 1972). Dapsone, Clofazimine, Ethionamide when tested individually had bactericidal activity and in combination potentiated each other's action. But no human experiments on combined therapy are reported. Patients under treatment with D.D.S. will have to be regular in taking treatment as long as necessary and the dosage used must be more than 50 mg. of D.D.S. per day.

It is also important and necessary to find new drugs that are cheap and easily administered to supplement D.D.S. It may not be very long before primary resistance to D.D.S. may emerge and there may be increasing number of patients who may not respond to D.D.S.

Further a method of treatment which will eliminate killed bacilli quickly from the body without producing harmful results should also be evolved.

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THE CLINICAL ASPECTS OF DAPSONE RESISTANCE

ROBERT R. JACOBSON

INTRODUCTION

It was probably a typical hot, humid, summer day in the early 1930's when a young Caucasian male with lepromatous leprosy was admitted to Carville for the first time. The diagnosis had been established two years earlier, and in the interval he had been on therapy with Chaulmoogra Oil with relatively poor results, and it is for this reason that he was referred here. Since nothing else was available to treat him, oral and injectable Chaulmoogra Oil were ordered for the patient and for a time he seemed to respond. Later his disease progressed in spite of continued therapy, however, and he gradually lost most of his sensation and eye sight. In the early 1940's he was among the first to receive the then new "wonder drug" for leprosy, the sulfones. His response was dramatic and over the next nine years his disease improved to the point of becoming inactive. Unfortunately, in spite of the fact that he continued on sulfoxone sodium as a prophylactic measure his disease reactivated a year later, and was no longer responsive to sulfone therapy. He was given other drugs but eventually died of renal failure, undoubtedly resulting from his longstanding active leprosy. This gentleman was probably the first, or certainly one of the first, patients infected with sulfone resistant bacilli.

In early 1972, a middle-aged Mexican-American male was admitted to Carville for the first time for initiation of therapy of recently diagnosed active border line leprosy. Routine mouse footpad drug sensitivity studies carried out prior to the start of dapsone revealed that some of this patient's bacilli appeared to be resistant to dapsone at the 0.0001% and 0.001% level of the drug in the diet of the mouse. This patient insofar as I know represents the first case where evidence of primary sulfone resistance was found on mouse footpad studies.

It has taken over three decades, but it now appears that we are in danger of losing one of our most effective weapons in the war against leprosy—the sulfones. What could we have done, and more important, what can we do now to prevent this?

HISTORICAL DEVELOPMENT OF PRESENT DAY ATTITUDES TOWARDS SULFONE THERAPY

Since one can hopefully learn from past mistakes, I think it would be worthwhile at this point to go back thirty-six years and trace the development of our present attitudes towards the sulfone therapy of leprosy. In this way we may be able to better answer such questions as: To whom should they be given; in what dosage, alone or in combination therapy; and for how long, and thereby stem the tide of sulfone resistant cases that threatens to engulf us.

The sulfones as a chemical entity has been known since 1908, but it was not until the late 1930's that medicine first took an interest in them because of their structural similarities to the earliest major antimicrobials, the sulfonamides. They were found to have a spectrum of activity similar to the sulfonamides, but unfortunately appeared to be too toxic for use against common bacterial infections because of the doses required. Later they were found to be effective against Mycobacterium lepraemurium and Mycobacterium tuberculosis infections in animals, and although they ultimately proved to be only mildly active against human tuberculosis infections this work stimulated interest in their possible usefulness against infections caused by other Mycobacteria—in particular leprosy.

In March 1941, then Faget and others undertook their now well known investigation of the activity of the sulfones against leprosy. They treated twenty-two patients with progressive borderline or lepromatous

leprosy and obtained good results in twenty-one, the only poor result being in a patient with progressive renal failure and severe reaction who received treatment irregularly. This work helped to establish the sulfones as the treatment of choice in leprosy and this is a position which they have never relinquished. Eleven of these original twenty-two cases are, by the way, still living. Eight continue to have active disease and five of these are known to be infected with sulfone resistant bacilli and the other three probably are. Three others harbored sulfone resistant bacilli at the time they died. This would give us a 50% incidence of sulfone resistance in this group and the figure might have been even higher had the other eleven lived longer.

Sulfone resistance was then of course far in the future, but although they were pleased with the results observed, several obvious problems were noted. First of all, although patients improved it was slower than that observed with anti-microbial therapy of almost any other disease. Secondly, if you stopped treatment the disease tended to relapse. Thirdly, although they had seen reactions before they now saw them more frequently, and finally Promin had to be given intravenously and oral therapy was obviously needed to make the treatment practical. Thus, over the ensuing years the dose of Promin was varied considerably and multiple new drugs were tried, but none proved to be successful on a long term basis, and in fact, until clofazimine was added in 1965, the only important anti-leprosy agents to be placed on Carville's Formulary were two other sulfones, sulfoxone sodium [Diasone(R)] and dapsone. The dosage of Promin employed in the 1940's ranged from a fraction of a gram daily to the fifteen grams daily (5 grams three times daily) employed in the so called "intensive promin" regimen. With diasone the dose was one-third of a gram three times daily and it is apparent that early in the sulfone era the inclination was to use higher doses though they did recommend a rest period of a week or more at regular intervals to avoid toxicity and "rest" the patient. Unfortunately it also allowed *M. leprae* to "rest". With the passage of time, however, the dosage employed gradually decreased for two reasons. First of all, initially the results of therapy seemed to be the same whether low or high doses were employed, and they reasoned that the danger of toxicity would be reduced with lower doses, though in fact they had relatively little in the way of toxicity problems with higher doses (some things such as renal amyloid or glomerulonephritis were occasionally falsely attributed to sulfone therapy). Secondly, leprous reactions of all types were (we now know incorrectly) attributed to the "toxic" effects of the sulfones and it was hoped that by starting the drug cautiously, lowering the maintenance dose or stopping therapy during severe reactions, the problem with reaction could be minimized. Unfortunately, neither they nor most others working with leprosy chemotherapy at that time ever evaluated this hypothesis in a well controlled trial. In the late 1950's, however, a number of patients began to show a diminished response to the sulfones and counter to the trend these were given higher doses again. Then in the 1960's Shepard developed his now well known technique for growing bacilli in the footpads of mice thereby offering us the means of doing drug sensitivity testing on *M. leprae* isolated from patients. This demonstrated for the first time in the laboratory that many of those treated early in the sulfone era were now infected with sulfone resistant bacilli. It also showed that *M. leprae* from untreated patients were incredibly sensitive to dapsone and paradoxically for a time accelerated the trend toward low dose sulfone therapy for leprosy.

Although the recommended dose of dapsone for lepromatous leprosy at Carville never got below 300 mg. per week, very low doses of the drug were used on a trial basis elsewhere. In general, the long term results of these trials were disappointing. Perhaps the best of them was that in the Karamui District of New Guinea utilizing DADDS. After three to five years of therapy relapse, or at least a cessation of improvement, was seen in some of the more active cases and it was concluded that DADDS alone was unsuitable therapy for multibacillary disease (Ref. 1).

Let us now consider briefly this trend toward lower doses of the sulfones from several different points of view to see if there was really any justification for it. First of all one might consider cost. Fortunately dapsone is one of the least expensive drugs available and cost probably was never a significant factor in this trend. Secondly, from the point of view of side effects there was likewise little justification to go to lower

doses. After over thirty years of usage and countless millions of doses, dapsone appears to be a relatively safe nontoxic drug even with the maximal doses used to treat this disease. Thirdly, there is the question of reaction and its relation, if any, to dosage. The question to be answered is, do the sulfones need to be started in very low doses and then gradually worked up to the desired therapeutic level? Originally, patients had been started on full doses of Promin or Diasone at Carville, but ultimately problems with reaction developed in many patients, and eventually the hypothesis was formulated that this problem might be avoided by the use of very low doses at first, and then increasing them slowly. This then became the standard practice at Carville, and many other areas of the world. As mentioned previously, as far as I can tell, no one ever evaluated this hypothesis in any well controlled trial, and a review of many of the old charts at Carville has demonstrated no particular benefit of this approach over the earlier one of starting full doses at once. More serious, however, was the fact that this same philosophy dictated that the dose of the sulfone be reduced or eliminated when severe reactions developed, and the iatrogenic irregular or prolonged low dose therapy that resulted with its coincident effect on patient attitudes is one of the reasons for the existence of a problem with sulfone resistance today. During the last decade this approach has gradually been abandoned at Carville for several reasons. In the first place, a number of studies have been done which, though representing adherents of both sides of the issue, in general demonstrate no benefit to beginning therapy with low doses of sulfones. Furthermore, the low dose approach is illogical if one considers how other anti-leprosy drugs are employed. Over the years Thiambutosine, streptomycin, clofazimine, ethionamide, and rifampin have all been used at Carville and in each instance these drugs were given in full doses from day one. No immediate reaction ever resulted and when reactions did occur, they were (with the exception of those on clofazimine which were milder) in general about as common and of the same degree of severity as those seen with the sulfones. Rifampin kills *M. leprae* more rapidly and the others with about the same degree of rapidity as the sulfones—why then were we so cautious with this one class of drugs? To answer this question, we began our own trials utilizing full doses of the sulfones from day one. Since 1971, nearly all lepromatous cases have been started on dapsone or dapsone with rifampin in full doses. We as yet have had no instances where an immediate reactive episode resulted and when reactions did occur several months after the start of therapy, they were no more frequent or severe than those observed in the past. Within the past year we have also began starting most non-lepromatous cases on full doses. To date we have had no immediate reactions, and again when they have occurred they are no more frequent or severe than those observed previously. Unfortunately, the great majority of patients we see have lepromatous disease so our numbers are small. The findings, however, are in agreement with those recently reported by Barnetson, Pearson, and Rees in the Lancet on sixty-eight Ethiopian patients (Ref. 2). Thus, at this time we feel it is safe to start most leprosy cases on full doses of the sulfones. This markedly simplifies therapy for physicians who treat few cases or for paramedical workers providing treatment in the field. The only danger with this approach would be the precipitation of a severe episode of hemolysis in some G-6PD deficient patients. This could be avoided with routine screening tests for G-6PD deficiency prior to treatment.

Finally, consider the metabolism and mode of action of the sulfones. Dapsone appears to be the only active form and the other sulfones are probably effective only insofar as they are converted by the body to this drug. Some patients (rapid acetylators) inactivate dapsone faster than others, but this is probably not important insofar as the likelihood of developing sulfone resistance is concerned (Ref. 3). The drug does have a relative long half-life (a day on the average) and it is this characteristic along with the low minimal inhibitory concentration of the drug for *M. leprae* that undoubtedly allowed us to use relatively low oral doses and broken schedules of administration (one to several days per week) for so long without getting into trouble with sulfone resistance sooner. Insofar as the mode of action of the sulfones is concerned, they are bacteriostatic and act via competitive inhibition with para aminobenzoic acid for an enzyme involved in the *De Novo* folate synthesis pathway of *M. leprae*. In such a process the degree of inhibition is then proportional to the concentration of the inhibitor, that is the sulfone related to the concentration of the natural substrate, namely para aminobenzoic acid. The exact mechanism by which resistance develops is uncertain, but it probably occurs

by a step wise process of mutation with the first generation mutants having only a low level of resistance and succeeding mutations gradually raising this level of resistance until a point is reached where only toxic sulfone levels would prevent growth of *M. leprae*. This is the pattern seen in many of our early sulfone resistant cases. Their bacterial load increased with progression of their disease, but this process was inhibited by higher doses of dapsone. Then later they became resistant to these with progression of their disease once more. At the point where possibly toxic levels of sulfones were needed to control the problem, we were forced to change their therapy initially to streptomycin and later to clofazimine.

This process can be followed nicely in the mouse footpads where initially resistance to the 0.0001% level of dapsone in the diet of the mouse occurs. Later, resistance to the 0.001% level and still later to the 0.01% level develops. At that point, their bacilli have in effect become fully sulfone resistant and further sulfone therapy is useless. The time for this progression from low levels of sulfone resistance to full resistance varies from patient to patient for reasons that are not clear. Our early data would indicate that this interval can be as short as one year or as long as seven or more years. It is thus clear that it would in theory, at least, be desirable to maintain dapsone levels at a high enough concentration to inhibit not only the original *M. leprae* population but also the first, second, third, etc. step mutants if one wanted to make a maximum effort to avoid the development of fully sulfone resistant strains.

CLINICAL FINDINGS IN SULFONE RESISTANT CASES

A review of Carville's more than 150 cases infected with sulfone resistant bacilli and a suitable group of controls has shown that with but few exceptions two factors were important insofar as the likelihood of this event occurring. That is, irregular intake of the sulfones and/or prolonged low dose therapy. By irregular therapy here we mean multiple breaks of one month or more in treatment and not just occasional missed doses. In fact, most of the periods off therapy were of several months or more duration. These were usually due to patient indifference, but many were iatrogenic; that is, were prescribed by the physician in the hope of controlling severe episodes of reaction. Prolonged low dose therapy, on the other hand, means intervals totaling a year or more where the dose of the sulfone used was maintained at a level equal to less than 100 mg. of dapsone or its equivalent in other sulfones per week. The interval from the start of sulfone therapy to the time of appearance of sulfone resistant strains has ranged from five years to over twenty years with an average of about seventeen years and the process as noted above is a step-wise one. It is undoubtedly this steadily increasing problem with sulfone resistance that has been the major factor in reversing the trend toward ever lower doses of dapsone mentioned earlier.

The following are typical case histories taken from our medical records. The first patient noted the onset of his disease at age 12. It was originally mis-diagnosed as acne, but eventually a diagnosis of lepromatous leprosy was established and he was referred to Carville. He was treated with 330 mg. of sulfoxone sodium daily and his disease became inactive in about eight years. He has minimal deformity of his hand as a result of his disease but works full time. He has contined his Diasone and his disease remains inactive 15 years later. The second case is a Chinese male who developed his disease while living in New York City. He took Chaulmoogra Oil at first, but when it ceased to have any effect in 1954 he came to Carville. He was treated at first with sulfoxone sodium 330 mg. daily and later with dapsone in a dose of 100 mg. four times weekly. His disease became inactive in 1960. He continued his dapsone, but in 1970, his disease reactivated and his bacilli were found to be sulfone resistant up to and including 0.01% Dapsone level in the diet of the mouse. That is, they were fully sulfone resistant. The third case came to Carville for the first time in 1958. She had lepromatous disease and was started on dapsone in a dose of 100 mg. six times weekly. She has been in and out of Carville many times since then and in the interval she was usually off therapy, and in fact had over twelve periods of more than one month off therapy. In 1970, her disease became progressive in spite of continued dapsone therapy and her bacilli were found to be fully resistant to the drug on the mouse footpad study. The fourth case was first admitted to Carville in 1963, with active lepromatous leprosy. She had a severe problem with ENL eventually develop, and over a period of several years was treated with an average of about 50 mg. of dapsone per week. In 1971 her disease became progressive in spite of continued now

high dose dapsone therapy, and a mouse footpad study showed that bacilli isolated from this patient were now fully sulfone resistant. The last case was admitted to Carville in 1975 with relatively early nodular lepromatous leprosy. He had a mouse footpad drug sensitivity study started and was discharged on 100 mg. of dapsone daily. He returned for follow up in five months. Though his lesions had flattened slightly, his BI on skin scrapings was unchanged and the MI still ran as high as 2%, findings which led us to question whether he had indeed been taking his dapsone as prescribed. He stated that he had done so and a blood sulfone level confirmed that at least at the time of his return he was indeed taking it. He was discharged to return when the drug sensitivity results became available. Two months later his mouse footpad studies returned and demonstrated evidence of resistance at even the highest level of dapsone (0.01%) in the mouse's diet.

These cases then represent the five different categories into which most lepromatous patients treated with the sulfones ultimately fall. The first represents the ideal and usual case. He was treated, his disease became inactive, and remained so on prophylactic Diasone. The second case represents perhaps the most frustrating aspect of sulfone therapy, and also fortunately the least common type. He took his therapy, his disease became inactive, and he continued faithfully on prophylactic dapsone. In spite of this his disease reactivated and was found to be sulfone resistant. Case three represents the more typical sulfone resistant case. She takes her therapy very irregularly or in low doses. Many of these do have their disease become inactive, but eventually they pay the price of their unconcern and their disease becomes sulfone resistant. The fourth case represents iatrogenic sulfone resistance. That is, its development was aided and abetted by the prescription of doses of dapsone that were much too low. The last case illustrates the problem with primary sulfone resistance. There are no clinical findings to indicate that the infection might be caused by sulfone resistant bacilli and the history is usually of no assistance because the case was newly diagnosed and had, therefore, never been treated before. When the case does not respond appropriately to treatment, the usual suspicion would be (as it was in this case) that the patient had just not taken his medicine as prescribed. The mouse footpad studies, of course, ultimately demonstrated the real reason for his poor response; that is, infection with sulfone resistant bacilli.

What clinical findings in any case should make one consider that the patient may be harboring sulfone resistant bacilli? First of all would be relapse in the face of apparent adequate sulfone intake. Secondly, a history of more than one year of low dose dapsone therapy; that is, 100 mg. or less per week. Thirdly, prolonged irregular sulfone intake. Fourthly, failure to attain bacterial negativity on skin scrapings and biopsy after more than ten years of apparently adequate sulfone therapy and, lastly, when relapse occurs in an older case or a newly diagnosed case is found after either has had prolonged contact with a known sulfone resistant case. Many of you familiar with the management of leprosy cases will, of course, be aware that relapse in the face of apparent adequate sulfone intake is in the majority of instances due to either inadequate intake or no intake at all. The point here however is that if this is so, then we are, in fact, dealing with irregular or low dose sulfone intake and these patients are prime candidates for the development of sulfone resistant disease in the future even if they have not already done so.

Examination of the skin may reveal the histoid type of lesions, but there is little else to set lesions caused by sulfone resistant bacilli apart from those caused by sulfone sensitive ones except that in the usual sulfone resistant case the lesions will be on skin showing evidence of old treated disease. I also have the impression that the disease is more rapidly progressive in the average sulfone resistant case than in sulfone sensitive ones, but I have no statistics to prove this, and the growth kinetics in the mouse footpad system are no different. Almost all of our sulfone resistant cases are lepromatous, but we have had a few borderline ones. In the case of primary sulfone resistance it could take any form, and we thus might see it in tuberculoid or indeterminate cases. This fact should be kept in mind especially by those working in areas with large numbers of known sulfone resistant cases or where the sulfones have been used to treat leprosy for more than 15 years.

THE DIAGNOSIS OF SULFONE RESISTANCE

Since a diagnosis of infection by sulfone resistant bacilli will necessarily lead to the abandonment of the least expensive, and

probably best, drug we have to treat this disease it should be made with great care. Ideally each case should have mouse footpad confirmation, but this is not practical in many areas of the world and, in fact, clinical suspicion of sulfone resistance by a physician familiar with the disease usually correlates very well with mouse footpad studies. If a patient's disease progresses in spite of a known adequate sulfone intake, then he can be considered to be infected with sulfone resistant bacilli. Insofar as the known adequate sulfone intake is concerned, it would be best if this were in the form of an injectable sulfone. In lieu of this, supervised oral intake or random blood sulfone measurements would probably suffice.

THE TREATMENT OF SULFONE RESISTANT LEPROSY

The treatment of sulfone resistant disease will be covered by other sections of this text, and I will mention only that nearly all patients at Carville infected with sulfone resistant bacilli are being treated with clofazimine alone, clofazimine plus ethionamide, or rifampin plus ethionamide. Rifampin should never be used alone to treat these cases since we have now had three of our cases on rifampin monotherapy relapse with rifampin resistant strains of *M. leprae* (Ref. 4). Perhaps clofazimine should also always be used in combination with another drug although we have had patients on it as monotherapy for up to twelve years now with no evidence of resistance having yet appeared.

THE PREVENTION OF SULFONE RESISTANT DISEASE

What might we do to prevent or at least reduce the incidence of sulfone resistant leprosy? First of all it makes sense to treat patients at all only if they can be treated properly. This means that follow up must be continued as long as is necessary to see that therapy is maintained—possibly for life with lepromatous cases. Secondly, dapsone should be given in full doses from day one of therapy and reduction of the dose or discontinuation of it should be avoided under any circumstances including reactive episodes. By full doses of dapsone I mean at least 50 and preferably 100 mg. of the drug daily in an adult. Thirdly, it is probably best to use dapsone in combination with one other drug for multibacillary disease. I say, "probably", because at this point we have no proof that the long term benefits of combination drug therapy will surpass those achieved with monotherapy, nor do we know which of the many possible combinations avaialble is most efficacious. The incidence of the sulfone resistant infections among our lepromatous patients is now in the vicinty of 10%. These as noted previously have occurred after an interval averaging 17 to 18 years from the start of therapy and the incidence might be considerably lower had all these patients been treated regularly with full doses of dapsone. Nonetheless, it is desirable to find other ways to reduce this incidence still further, both to avoid the damage to the patient that prolonged activity of their disease can produce and also to avoid an epidemic of primary sulfone resistant cases resulting from contact with these patients. For this purpose, combination therapy by analogy with the treatment of tuberculosis would seem to be the logical path to follow. As an added bonus it hopefully might reduce the length of treatment required by a lepromatous case from life to some finite number of years. Finally, there is the matter of patient education. Unless a patient knows something about his disease, why it is being treated, and what to expect from treatment in the way of reactions, clearance of his skin lesions, etc., he will be unlikely to cooperate fully with his doctors. The aspect of patient care cannot be emphasized enough because if the person responsible for the patients' care does not provide him with what he needs to know about his disease, older patients will offer him endless bad advice. A short time spent on patient education at the start of treatment will return benefits to the patients and leprosy control program for many years to come.

SUMMARY

Sulfone resistant leprosy has become a problem of steadily increasing magnitude over the past 15 years. It should be suspected in any patient whose disease relapses on appropriate therapy. Most cases will have a history of irregular intake of the sulfones or prolonged low dose sulfone therapy. Mouse footpad confirmation of the diagnosis is desirable, but impractical on a large scale and unnecessary in the usual case. Regular intake of full doses of dapsone, perferably in combination with another anti-leprosy drug, holds the greatest promise at this time of halting what is rapidly becoming a problem of epidemic proportion.

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LEPROSY

CHAPMAN H. BINFORD, WAYNE M. MEYERS

Definition. Leprosy, a chronic infectious disease caused by *Mycobacterium leprae*, affects principally the cooler parts of the body, especially the skin, upper respiratory tract, certain peripheral nerves, testes, and the anterior part of the eyes.

The Infectious Agent. The morphology and staining of the leprosy bacillus resembles *Mycobacterium tuberculosis*, but *M. leprae* is less acid-resistant. Differing from other mycobacteria, it oxidizes D-dopa and after pyridine extraction loses its acid-fastness. In well developed lesions of lepromatous leprosy, the bacilli characteristically form compact, rounded intracellular masses (globi). Hansen first saw and described the leprosy bacillus in 1873 and reported his observations in 1874; now, a century later, *M. leprae* still has not been acceptably grown *in vitro*.

Prevalence and Epidemiology. The World Health Organization estimates that leprosy afflicts nearly 11 million people. The distribution is shown in Fig. 1. Today, most patients live in the tropics but leprosy is not a tropical disease; during the middle ages it prevailed throughout Europe. In the United States, most cases are reported from California, Florida, Hawaii, Louisiana, New York City and Texas. Approximately half of these patients were infected outside the USA. There are approximately 2,600 known patients in the USA; in 1974, 101 new cases were reported.

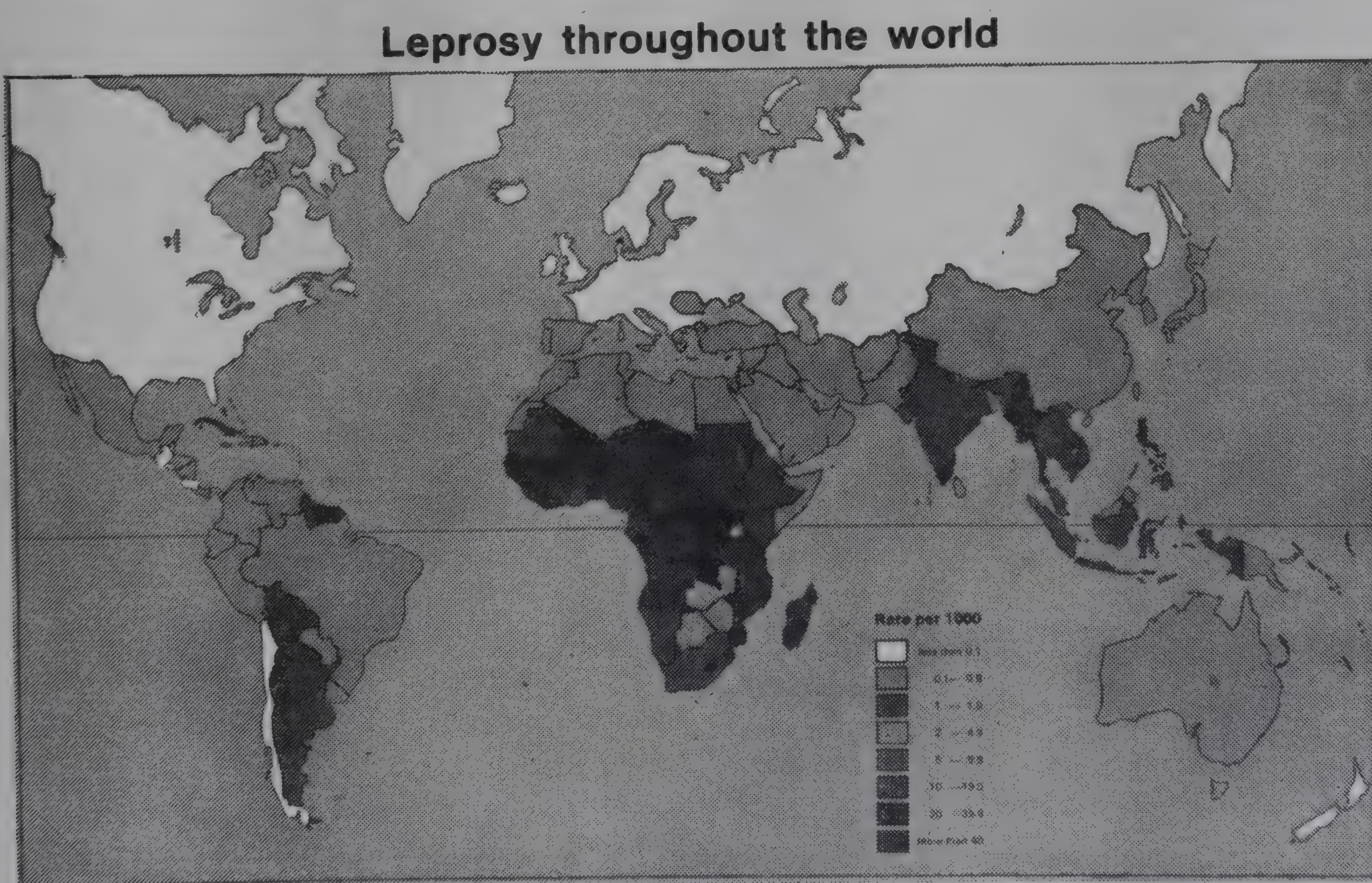


Fig. 1. **Leprosy throughout the world.** AFIP 75-4786. (Courtesy of Drs. Luiz Bechelli and Dominguez Martinez. Published in WHO Bulletin, 34 : 811, 1966. Reprinted in WHO World Health, October 1971.)

Persons of any age may become infected, but in areas of high endemicity most cases are diagnosed in the first 3 decades. The opinion prevails that leprosy is spread by direct contact through the skin or the mucous membranes of the mouth or nose, without aid of an insect vector or an intermediate host. Patients with moderately advanced or advanced untreated lepromatous leprosy shed numerous bacilli from even minor abrasions and in nasal discharges. Patients with tuberculoid or borderline-tuberculoid leprosy in reaction can also shed bacilli from lesions, however, it is doubtful that leprosy is transmitted from tuberculoid lesions which are not in reaction. The generally accepted incubation period is 3 to 5 years but may be shorter or longer. Most people resist infection. For instance, the attack rate of healthy spouses living with infected, untreated mates is usually given as 5 to 6%. Lara, in the presulfone era, at the large Culion Leprosy Hospital in the Philippines, studied children who had lived intimately with patients. In 1938, he reported early lesions in about 30%; most of these lesions healed spontaneously, and chronic progressive leprosy developed in only about 8%.

Members of the U.S. Armed Forces serving in countries where leprosy is endemic occasionally become infected, but lesions may not be apparent for many years. During the period 1940 through 1968, 46 known infections were reported in U.S. veterans who had not lived in endemic areas prior to entering military service.

Transmission to Animals. Shortly after Hansen discovered the leprosy bacillus, numerous attempts were made to transmit leprosy to several different species of animals. In 1958, Gunders in Liberia inoculated a chimpanzee intravenously with *M. leprae.* After 11 months numerous dermal lesions developed; they contained acid-fast bacilli and histopathologically resembled borderline leprosy. This was probably the first successful transmission of human leprosy to an animal. Successful transmission to rodents was not achieved until investigators became aware that in man the leprosy bacilli grew best in tissues with temperatures several degrees lower than that of internal organs.

In 1960, Shepard demonstrated multiplication of *M. leprae* in foot pads of mice. Binford (1961) reported mild lesions in the ears of golden hamsters, and later, in ears and foot pads of Chinese hamsters, cotton rats, and *Mystromys.* Infection of nerves, a characteristic feature of human leprosy, was also present in these rodents. Rees and associates (1966) reported macroscopic and disseminated lesions in mice immunosuppressed by thymectomy and total body irradiation (900r).

In 1971, at the Gulf South Research Institute in New Iberia, Lousiana, an armadillo, *Dasypus novemcinctus,* developed a severe disseminated infection which closely resembled lepromatous leprosy. Storrs subsequently reported that as determined by biopsy or autopsy, about 40% of inoculated armadillos developed infections; at the AFIP, histopathologic studies on 30 armadillos confirmed the disseminated lepromatous-like nature of these infections. Nerves in infected armadillos contained acid-fast bacilli. The susceptibility of the armadillo to *M. leprae* is unique and probably related to its body temperature of 32 to 35C. This is the temperature range of human tissue in which *M. leprae* flourishes in a susceptible patient.

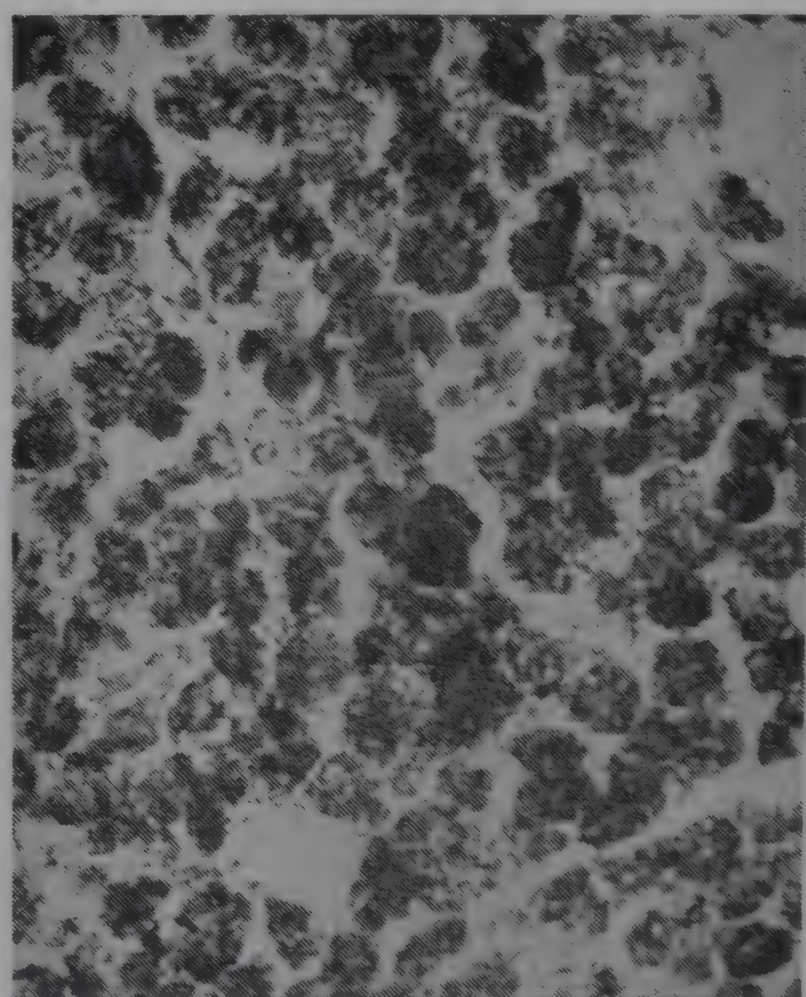


Fig. 2. Leprosy in the nine-banded armadillo. Nodule in deep skin of an armadillo inoculated intravenously 26 months before autopsy. The macrophages are packed with acid-fast bacilli. Fite-Faraco, X660, AFIP 74-12218.

Classification and Clinical Features. Leprosy has been classified into two principal types—lepromatous and tuberculoid—representing opposite poles of the patient's immunologic response. An intermediate form, called borderline (dimorphous), develops in patients whose cellular resistance lies between the 2 major types. When the disease is too early or two mild for classification, it is called "indeterminate leprosy".

Ridley and Jopling have developed a practical classification of leprosy based on clinical, bacteriologic, and histopathologic observations correlated with lepromin reactivity. As a result of their studies the following principal groups have become well recognized: Lepromatous (LL), borderline-lepromatous (BL), borderline (BB), borderline-tuberculoid (BT), and tuberculoid (TT).

In lepromatous leprosy, cellular resistance against *M. leprae* is minimal. Bacilli multiply abundantly within macrophages causing swelling of the skin by their sheer numbers. In tuberculoid leprosy, cellular immunity is pronounced and manifested by an extensive epithelioid cell and lymphocytic reaction, even though only a few bacilli are present. Clinically and histopathologically, borderline leprosy has characteristics of both tuberculoid and lepromatous leprosy. Even when the lesions and histopathologic features are not sufficiently developed to permit classification, a diagnosis of indeterminate leprosy is possible if dermal nerves are invaded by acid-fast bacilli.

Clinically, there are macular or infiltrated lesions in all the major classes of leprosy. The patient with lepromatous leprosy may present a variety of skin lesions that range from slightly erythematous or hypopigmented macules to papules, nodules, plaques, or diffuse infiltrations. The borders of lepromatous lesions are not sharply defined, and later, they become confluent. In some patients, virtually the entire skin becomes involved

Fig. 3. Advance of lepromatous leprosy in a 13 year old Hawaiian in the presulfone era. The above photograph shows the patient on admission in 1931. The photograph to the right was taken in 1933. Had sulfone drugs been available on admission, the disease would have not progressed but would have regressed and probably become bacteriologically negative after several years of treatment, AFIP 75-2479-2.

Fig. 4. Lepromatous leprosy in a woman from Uganda. Note nodules over the face, a generalized infiltration of the ear and loss of eyebrows. AFIP 69-3569.

Fig. 6. Lepromatous leprosy. Lepromatous infiltration of ear of an adult Zairian man. The luxuriant growth of bacilli in the ear in lepromatous leprosy is probably related to the coolness of this area. AFIP 75-15603.

Fig. 5. Advanced lepromatous leprosy in a Hawaiian girl, age 6. This patient who lived before sulfone was used would have a life expectancy of less than 3 years. AFIP 75-15806.

Fig. 7. Lepromatous leprosy. There are advanced lepromatous lesions over most of the body, and gynecomastia in this adult Zairian man. Gynecomastia, seen frequently (6 to 19%) in chronic lepromatous leprosy, is most probably related to severe leprotic orchitis. AFIP 75-15600.

(colour Fig. 1). Loss of eyebrows, beginning laterally, is common in advanced lepromatous leprosy and is a useful diagnostic feature.

The lesions of early lepromatous leprosy are usually only mildly hypesthetic but, when advanced, may be anesthetic. Light touch and heat-cold discrimination are the most useful routine tests for determining cutaneous sensory changes.

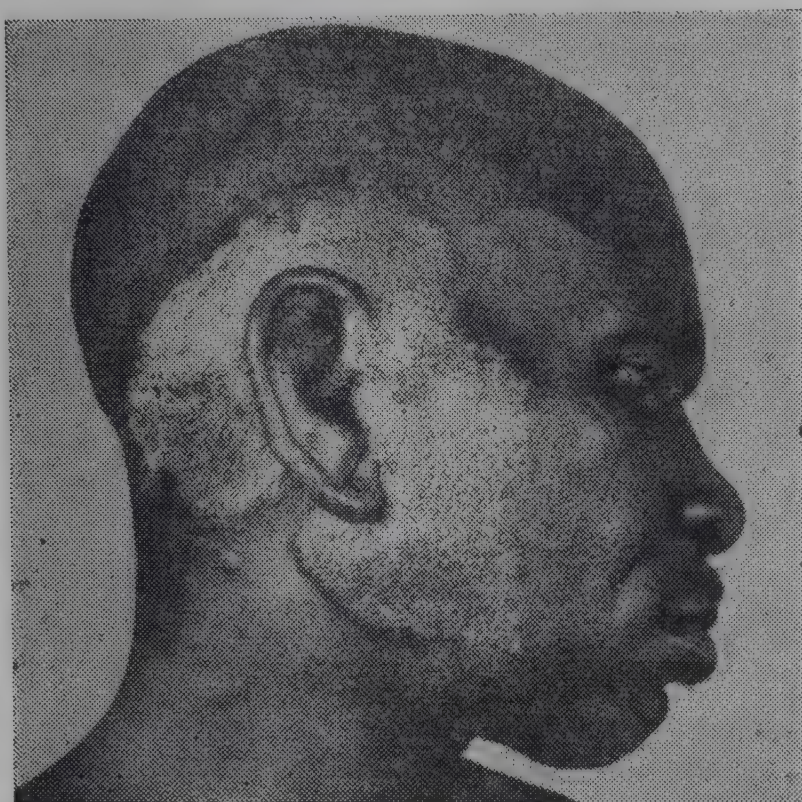


Fig. 8. Tuberculoid leprosy. An anesthetic plapue with well defined edges and scaly surface extends over the cheek and into the scalp in a man from Zaire. While the scalp is very resistant to other forms of leprosy, it may be involved in tuberculoid leprosy. AFIP 75-2905-1.

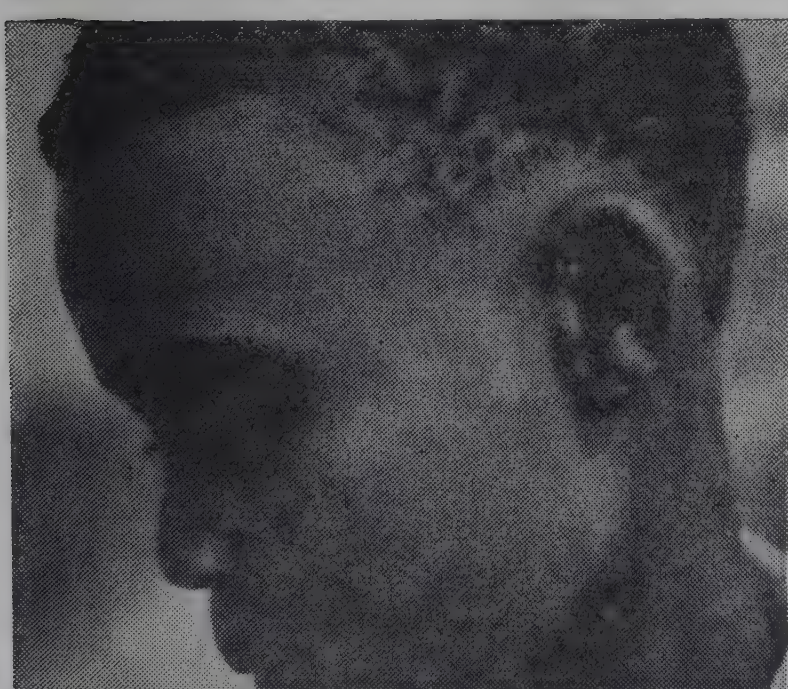


Fig. 9. Tuberculoid leprosy. Early lesion showing well defined papulated borders in a 12 year old boy in Zaire. The lesion was anesthetic. AFIP 75-15598.

Fig. 10. Tuberculoid leprosy. Advanced lesion showing well defined border and healed, repigmented, anesthetic center in a Zairian woman. AFIP 75-15593.

Fig. 11. Ring lesions of tuberculoid leprosy in Caucasian patient in a period of reaction. The borders are papular, elevated, and erythematous. Within the rings the lesion has "burned out," leaving atrophic anesthetic skin. AFIP 75-12821-1.

The early lesions of tuberculoid leprosy are sharply defined, slightly erythematous, or hypopigmented macules in which sensation is definitely impaired. As these lesions progress,

the borders become elevated and erythematous, while the centers are flat and hypopigmented. Repigmentation in the central areas of tuberculoid lesions is an indication of healing.

Borderline lesions begin as macules or small plaques with elevated centers. Later, the central area may flatten and peripheral areas become elevated, circinate, or serpiginous. The borders are variable, sometimes well defined, and sometimes vague. Sensory changes are usually readily demonstrable. Borderline lesions with predominant tuberculoid features are called borderline-tuberculoid (BT) and, when lepromatous changes are prominent, are classified borderline-lepromatous (BL).

Principally in patients of Mexican origin, there is a form of leprosy characterized by diffuse involvement of the skin without elevated lesions. This interesting variety of lepromatous leprosy is called Lucio or "spotted" leprosy. These patients may develop a necrotizing obliterative vasculitis with multiple skin ulcers. This phenomenon was first described by Lucio and Alvarado in 1852 (Color Fig. 8).

In 1963, Wade described a form of lepromatous leprosy with lesions resembling dermato fibromas or neurofibromas. Most of these lesions were in patients who for many years had received only intermittent treatment with sulfone drugs. He called this the "histoid" variety of lepromatous leprosy. Some authorities associate "histoid leprosy" with sulfone resistance but this relationship is not established.

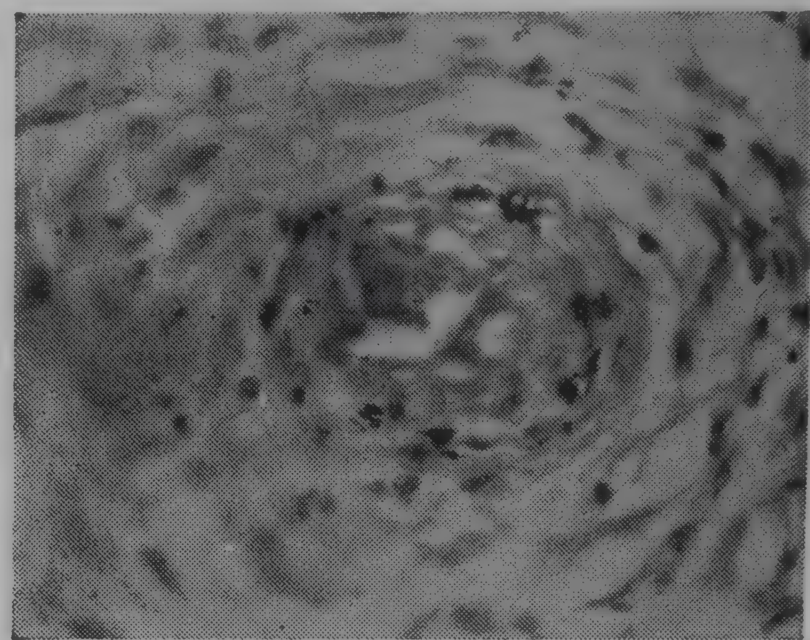
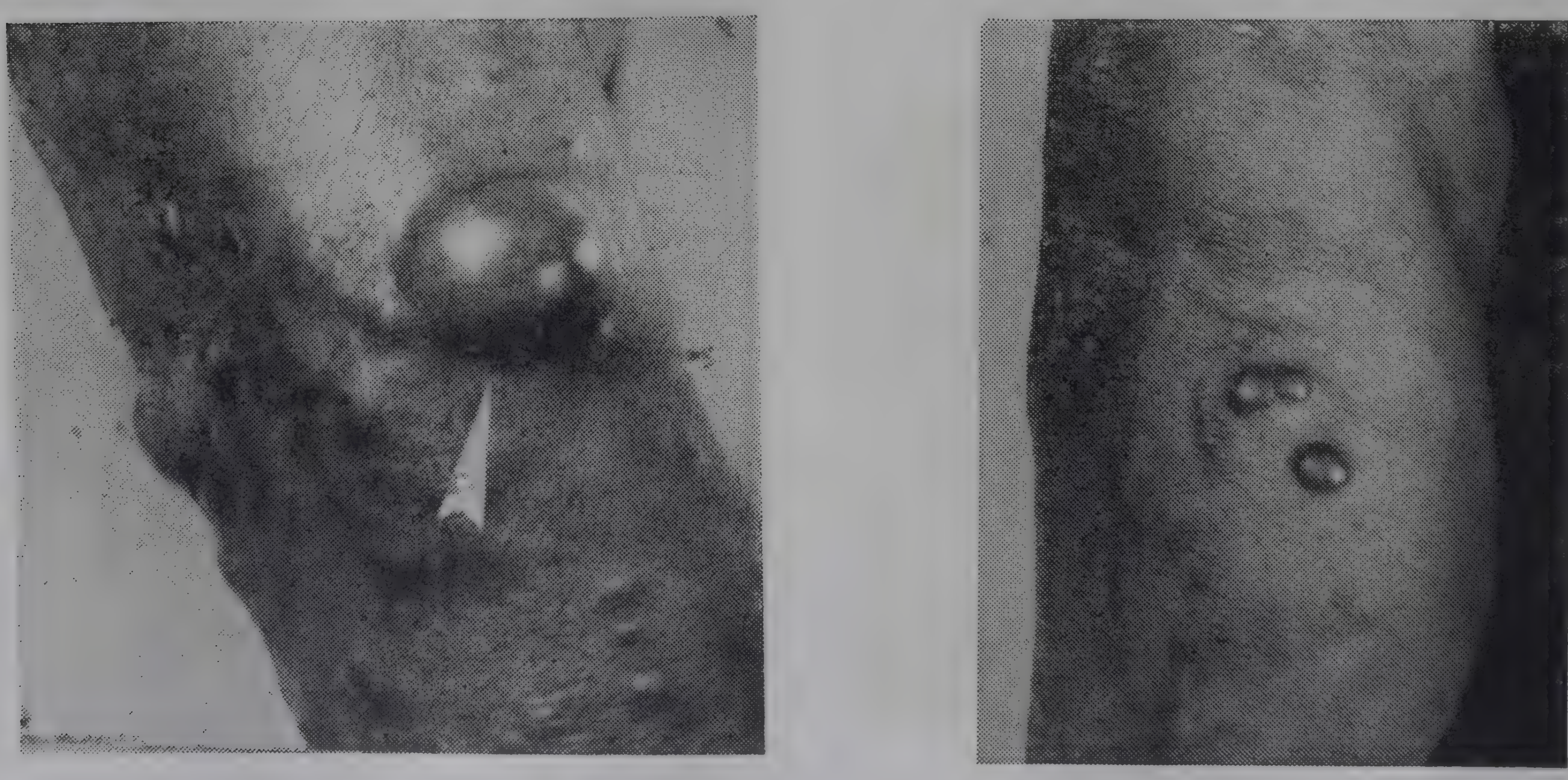


Fig. 12. Small artery in skin of a patient with lepromatous leprosy of the Lucio variety. The obliterative leprotic vasculitis causes small triangular infarcts of the skin. See clinical lesions in Color 8. Fite-Faraco, X630, AFIP 57-9794-1.



(A) (B)

Fig. 13. Histoid variety of lepromatous leprosy. **A & B,** dome-shaped, firm nodules of arms. **A.** AFIP 75-2629-2. **B.** AFIP 75-2629-1.

Fig 13. C, numerous firm nodules of back. These lesions were in Filipino patients who had been irregularly treated with sulfone drugs for many years. C. AFIP 75-15876-1.

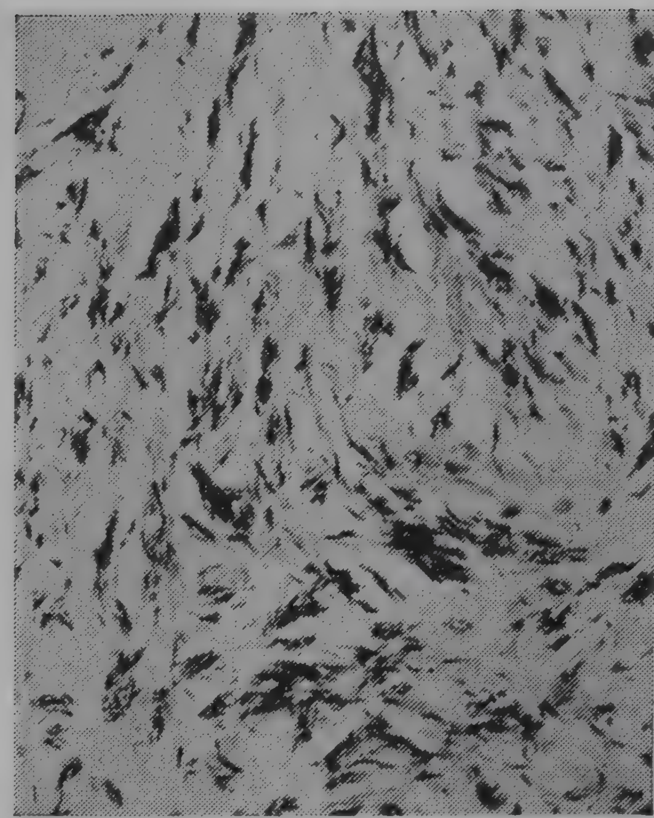


Fig. 15. A Fite-Faraco acid-fast stain of replicate section shown in Fig. 14. Solidly stained bacilli are arranged parallel to the long axis of the spindle cells. X530, AFIP 68-8626.

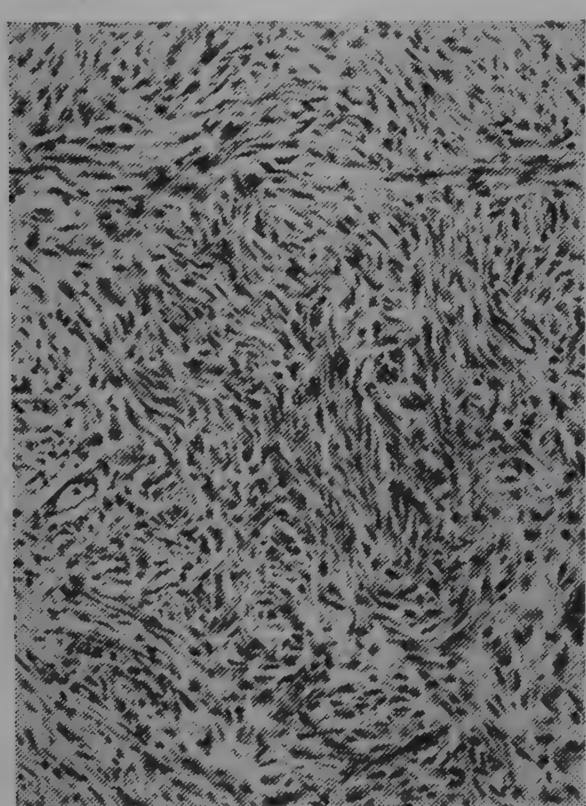


Fig. 14. The histopathologic pattern of intertwined fascicles of spindle cells resembles that of dermatofibroma. X175, AFIP 75-15876-2.

Reactions in Leprosy. Patients with lepromatous leprosy may have acute exacerbations characterized by bouts of high fever, enlargement and reddening of all lesions, enormous increases in bacilli and the development of new lesions. In tuberculoid leprosy, reactions are manifested by reddening and elevation of lesions, the development of new lesions and are sometimes accompanied by painful neuritis. Lesions which previously contained no bacilli may, in reaction, contain many bacilli. Patients with tuberculoid leprosy may be infectious during reactions. Similar reactions are common in patients with borderline leprosy. Painful, damaging neuritis is a frequent serious complication of reactions in borderline leprosy.

Erythema Nodosum Leprosum (ENL). In patients with lepromatous or near lepromatous leprosy, especially in those receiving effective chemotherapy, erythema nodosum may be a severe and disabling complication. This reaction, which is probably a manifestation of immune complex formation, is characterized by the outcropping of many erythematous, deep, tender nodules in the skin. These nodules often disappear in a week or two. This reaction resembles erythema nodosum that complicates other diseases, but the special term, erythema modosum leprosum (ENL), is used. Recurrent attacks are common (Color Fig. 7).

The Lepromin Test. The lepromin test, introduced by Mitsuda in 1919, is performed by the intradermal injection of heat-killed *M. leprae* obtained from lepromatous tissue. Patients with lepromatous leprosy are nonreactive, but patients with tuberculoid leprosy have a papulonodular reaction which is maximal in 3 to 4 weeks (Mitsuda reaction).

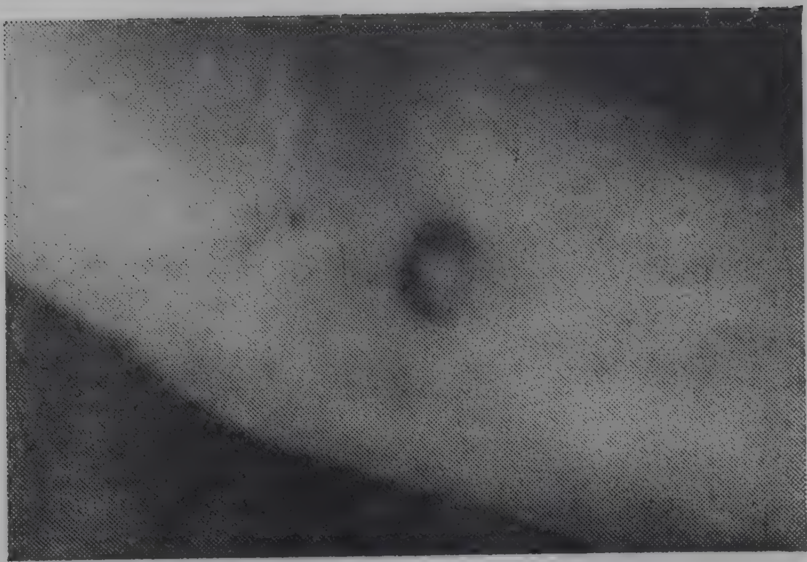


Fig 16. Lepromin reaction. This is a positive Mitsuda reaction in the forearm of a tuberculoid leprosy patient, four weeks after injection of lepromin. AFIP 55-12646.

Histologically, the reaction is an epithelioid cell granuloma. In some tuberculoid patients, 24 to 48 hours after the Mitsuda antigen is injected, an erythematous reaction resembling a positive tuberculin test develops (Fernandez reaction).

Dharmendra prepared an antigen by extracting chloroform-soluble material and bacilli from lepromatous tissue. When injected into the skin of tuberculoid patients, a local erythematous induration follows in 24 to 48 hours.

A positive lepromin test to the Mitsuda or Dharmendra antigens denotes a cell-mediated reaction to *M. leprae* or its products. The lepromin test is very important in prognosis because it assesses the immunologic status of the patient. Most normal adults in all parts of the world react positively to lepromin. Because of these positive reactions in patients without leprosy, the use of the lepromin test as a diagnostic aid may lead to serious erroneous diagnoses and even to malpractice actions.

Histopathology. In **lepromatous leprosy,** early lesions show proliferating macrophages (histiocytes) around blood vessels, nerves, and dermal appendages. As the lesion progresses, the macrophages become filled with *M. leprae* and may eventually replace and thicken the dermis. Although the infiltrate may be massive, a thin, uninvolved subepidermal "clear zone" persists immediately beneath the basal layer. The infected macrophages are supported by a delicate stroma, and the lesion is supplied by a rich network of capillaries. Old, infected macrophages develop lipid vacuoles and appear foamy. Such macrophages characterize lepromatous leprosy and are called Virchow lepra cells. In developing lesions, bacilli are frequently arranged in parallel bundles. Later, dense masses of bacilli (globi) replace the entire cytoplasm. When the wall of an infected cell degenerates, the released bacilli may coalesce to form large acid-fast masses; they may in turn be enclosed in giant cells (giant globi). In lepromatous leprosy, many bacilli are within small dermal nerves that are otherwise normal. They also invade the endothelial cells of capillaries and larger blood vessels, walls of blood vessels, arrectores pilorum muscles, and epithelial cells of of hair follicles.

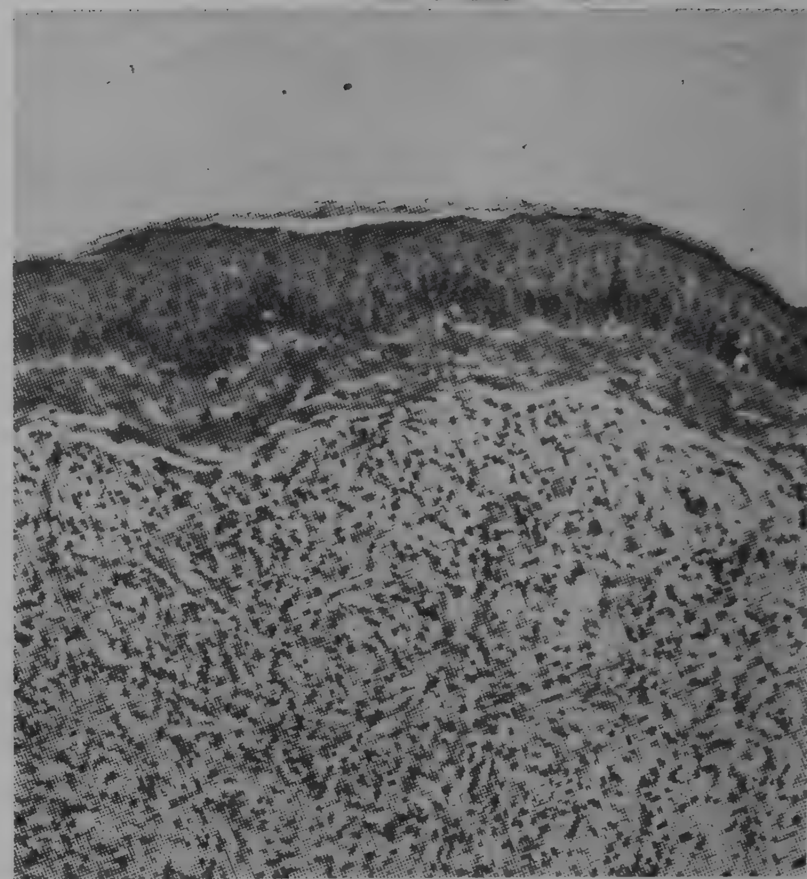


Fig. 17. Lepramatous leprosy, skin. The "clear zone" separating the infiltrate from the epidermis is well demonstrated. The infiltrate consists of moderately foamy histiocytes. There are some round cells which suggest that the lesion was reactive when the biopsy was made. Numerous leprosy bacilli were in the histiocytes. X 145, AFIP 65-1653.

The lesions of erythema nodosum leprosum (ENL) are usually in the lower dermis and adjacent subcutis and consist of focal infiltrations of neutrophils and other inflammatory cells. An allergic type of vasculitis is usually present. There is no exacerbation of the lepromatous infection during the ENL reaction.

In **tuberculoid leprosy,** the most characteristic feature is the infiltration of epithelioid cells and lymphocytes in cords or clusters. Langhans giant cells may be present. Lesions

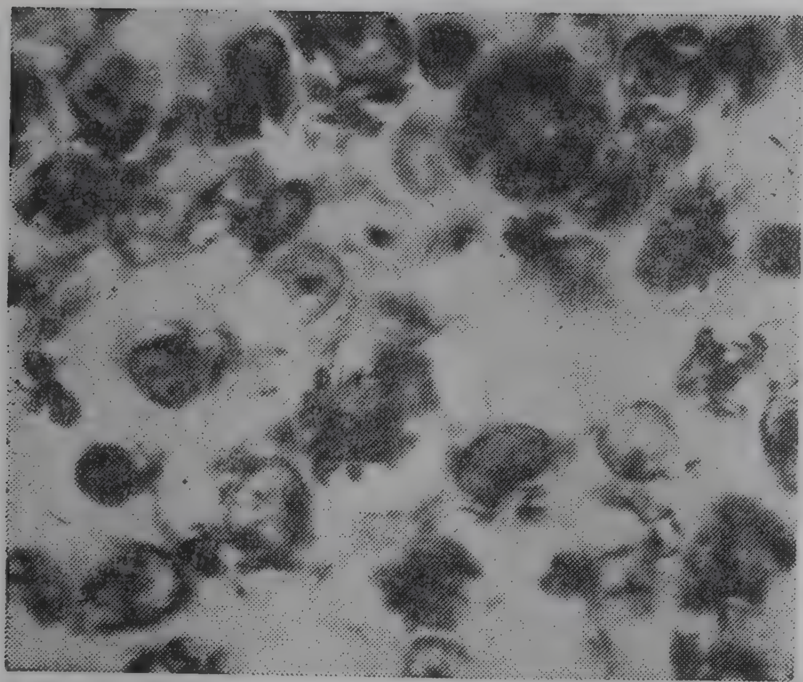


Fig. 18. Lepromatous leprosy, skin. Observe the numerous intracellular bacilli within the macrophages. Fite-Faraco, X920, AFIP 56-19549.

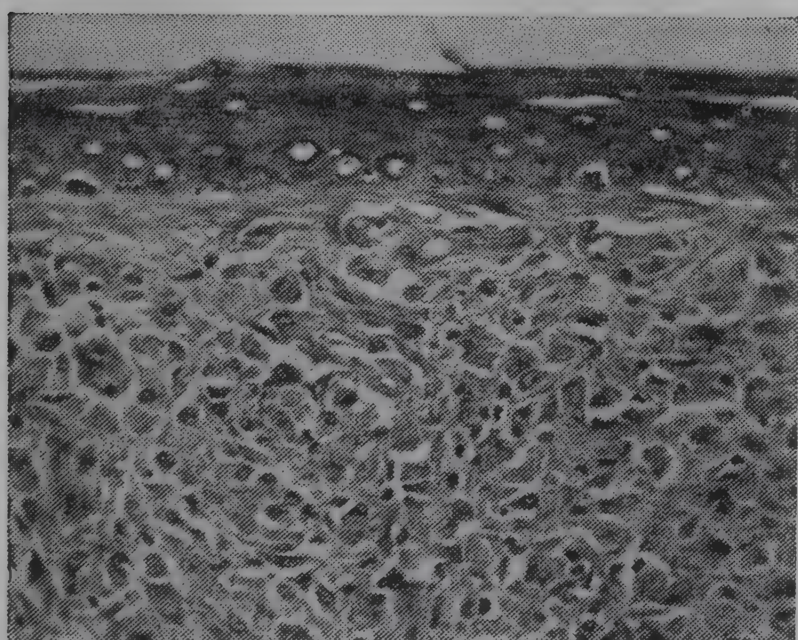


Fig. 19. Lepromatous nodule of skin. The infiltrate at this site has compressed the "free zone" but does not extend to the basal layer of the epithelium. The infiltrate consists of clearly defined slightly vacuolated histiocytes. X350, AFIP 74-2725.

of tuberculoid leprosy resemble Boeck's sarcoid, noncaseating tuberculosis, and other diseases in which there are epithelioid cell granulomas. Usually, the upper dermal infiltrates of tuberculoid leprosy extend into the papillary stroma and touch the basal cells of the epidermis, thus differing from lepromatous leprosy by the absence of a "clear zone".

Extensive epithelioid and mononuclear cell infiltration of dermal nerves is a distinctive feature of tuberculoid leprosy. Schwann cells may be prominent. Bacilli, if present. are usually within remnants of nerve fibers.

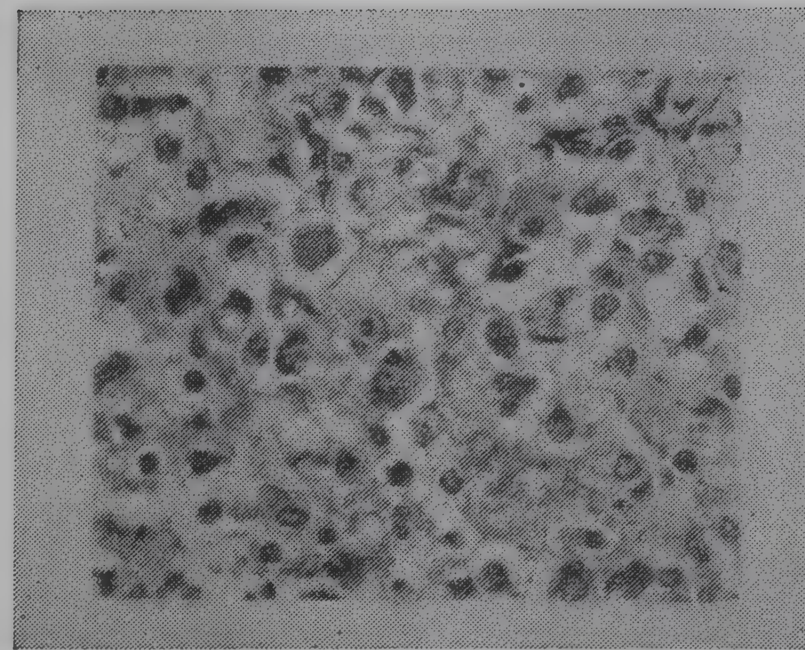


Fig. 20. Lepromatous leprosy, skin. The arrow points to a vacuolated histiocyte containing a globus stained by hematoxylin. AFIP 75-15878.

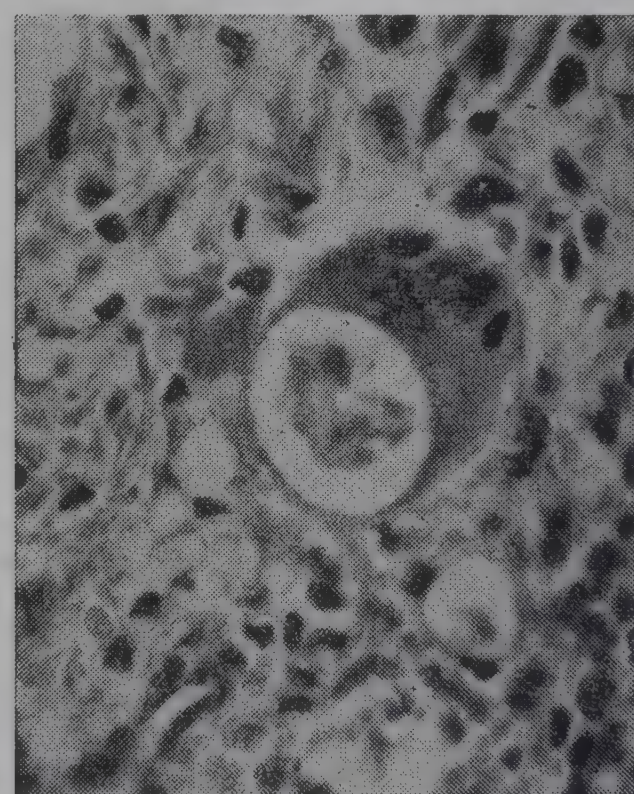


Fig. 21. Giant globus, lepromatous leprosy. When histiocytes containing globi disintegrate, the masses of old bacilli become a "foreign body" in a giant cell and are well demonstrated in H & E stained sections. X800, AFIP 57-5284.

In some lesions, a search of many sections may be required to find a single bacillus. In reactive tuberculoid leprosy, however, bacilli may be readily found in the edematous epithelioid cell infiltrate. In some biopsy specimens from old tuberculoid lesions no nerves are seen.

In the **borderline group**, a single section may contain macrophages with bacilli and focal aggregates of epithelioid cells. The nerves may reveal varying degrees of intraneural cellular infiltration, and frequently contain

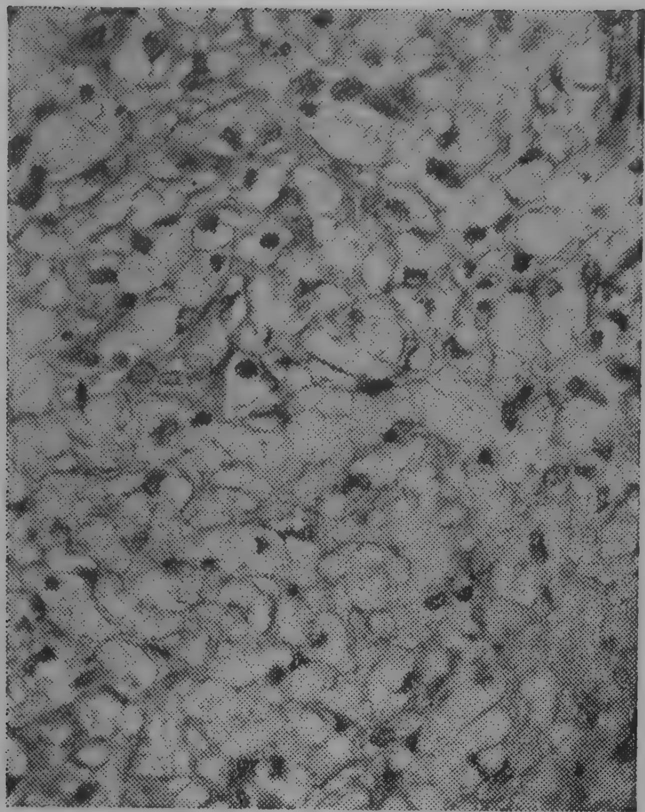


Fig. 22. Old lepromatous leprosy. In very old lesions of leprosy, especially in patients who have been treated with effective drugs, the lesions histopathologically resemble xanthomas. X475, AFIP 54-18769.

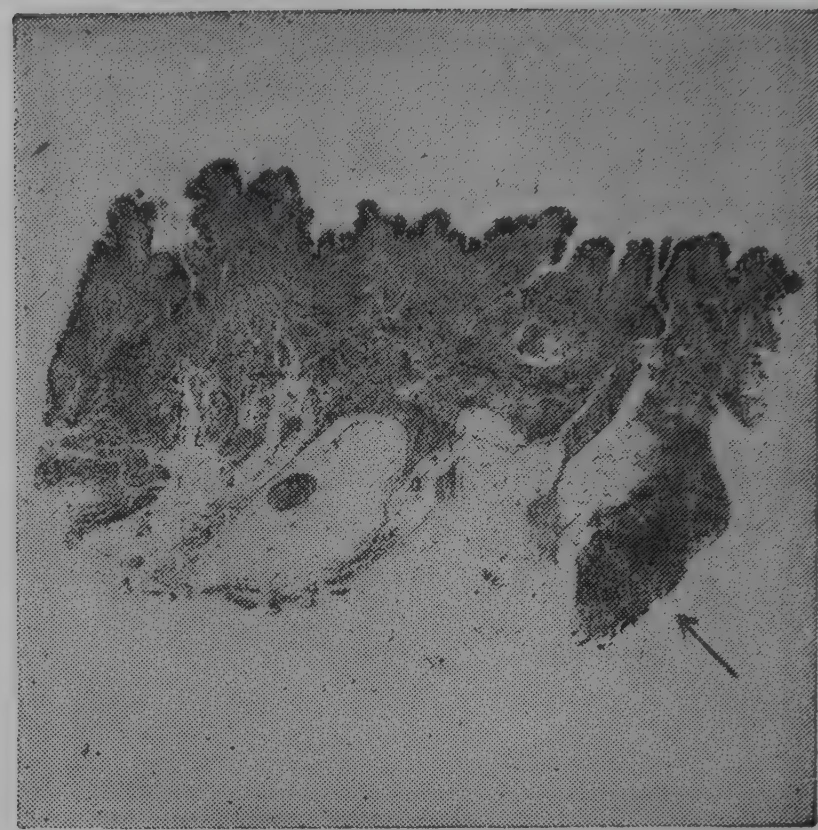


Fig. 24. Erythema nodosum leprosum (ENL). The arrow points to a necrotizing lesion. The lower dermis, under higher magnification, showed there was vasculitis accompanied by polymorphonuclear infiltrate. X14, AFIP 72-12475.

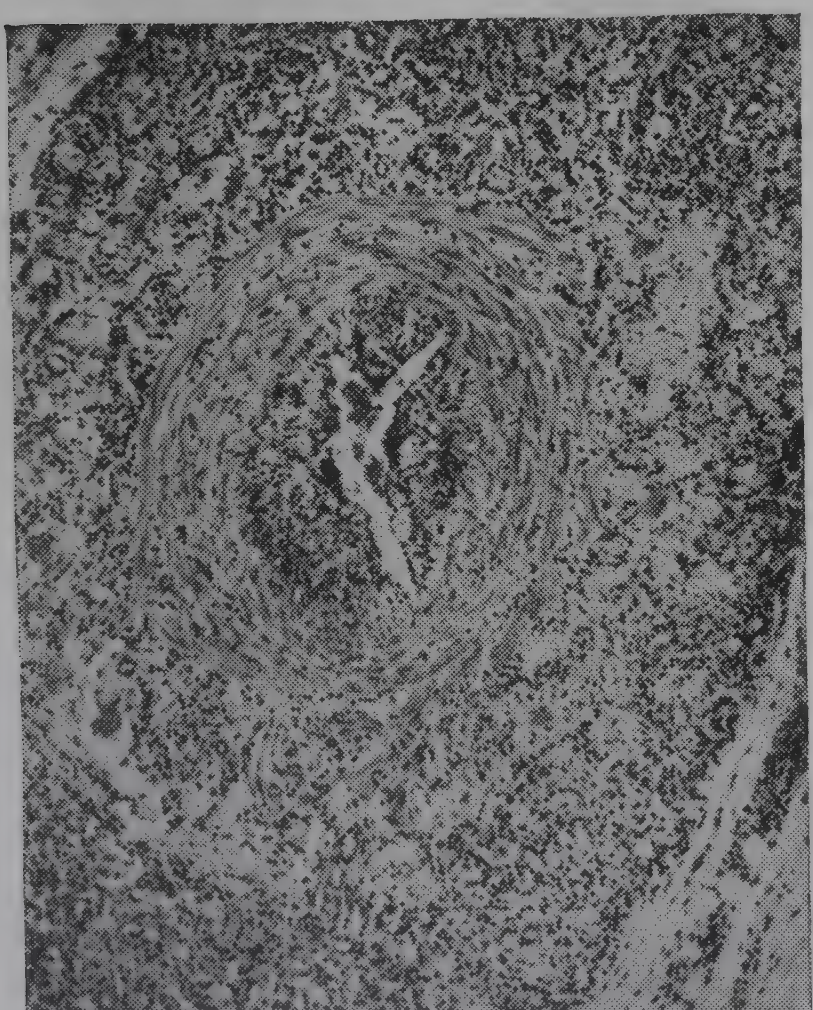


Fig. 23. In severe untreated lepromatous leprosy there may be severe arteritis. In the thickened walls and subintimal tissues of this artery there were many bacilli. X100, AFIP 74-12821-3.

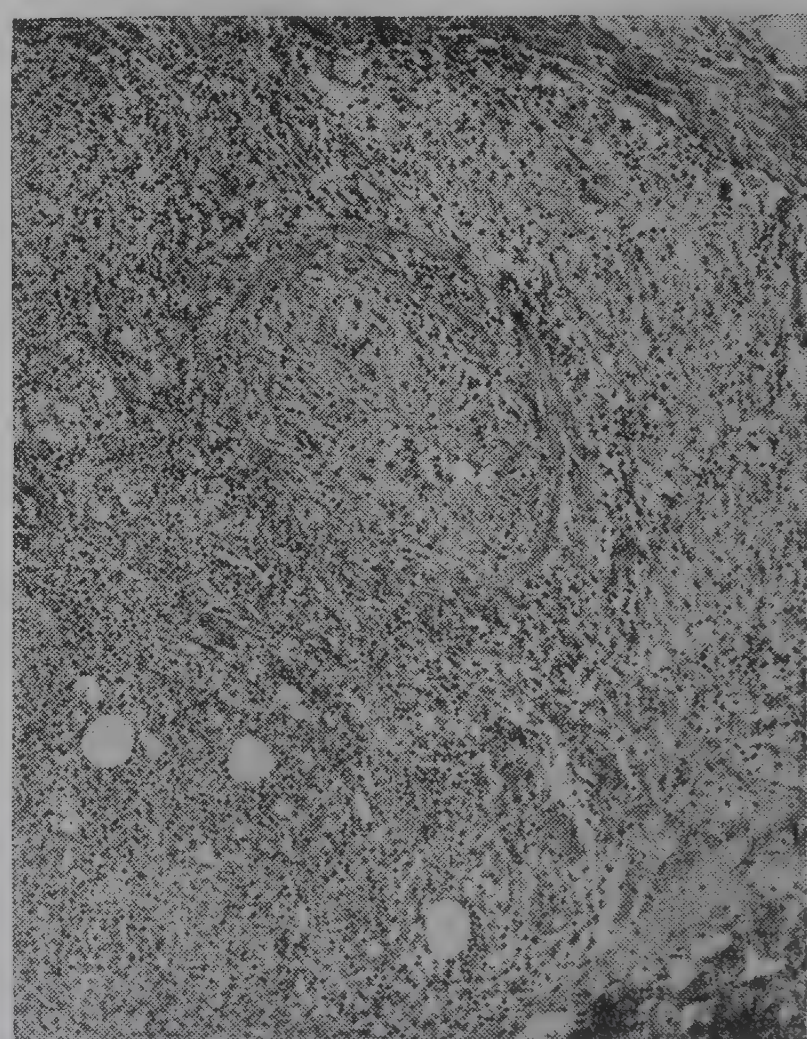


Fig. 25. An early ENL lesion (72 hours) showing obliterative arteriolitis and dense inflammatory infiltrate, predominantly neutrophils. X115, AFIP 64-1412.

Fig. 26. Tuberculoid leprosy. Observe the dense infiltrate of the dermis that extends to the epidermis. The arrow points to a group of destroyed nerves which are shown at higher magnification in Fig. 27, x 13, AFIP 72-12492.

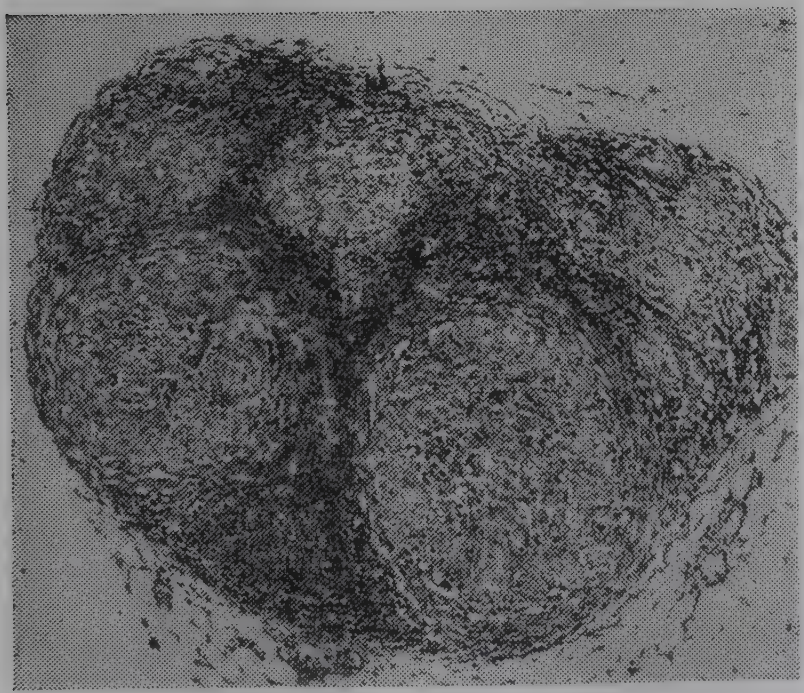


Fig. 27. Higher magnification of lesion indicated by arrow in Fig. 26. The epithelioid cell cords contain remnants of nerve in which an occasional bacillus was seen. Dense lymphocytic infiltration surrounds the cords of epithelioid cells. X65, AFIP 72-12463.

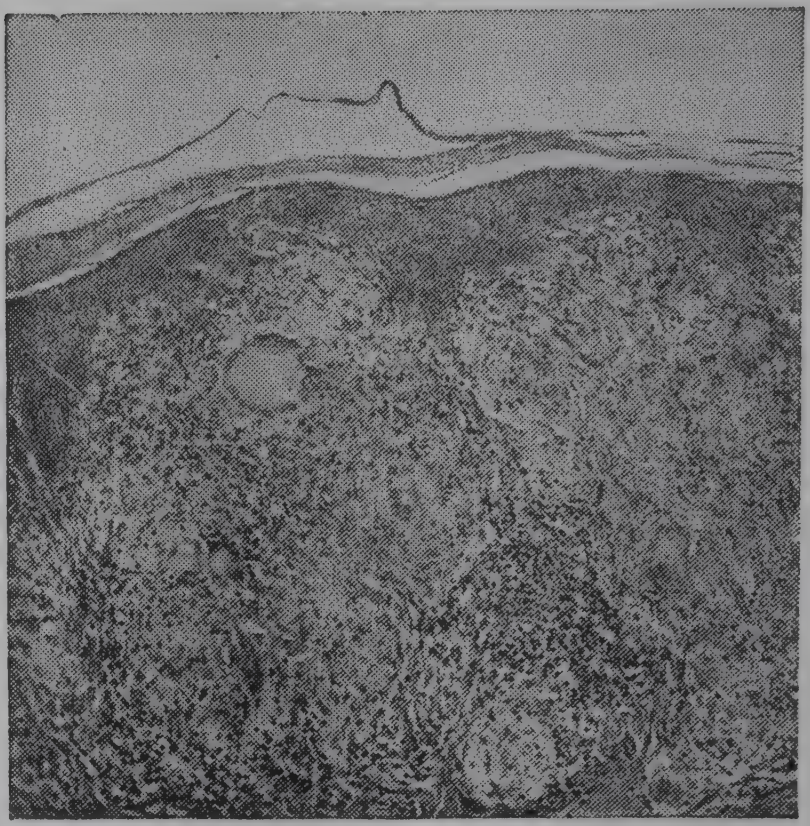


Fig. 28. The dense infiltrate shown in Fig. 26 is seen under higher magnification to be composed of epithelioid cells, Langhans giant cells, and lymphocytes. Note that there is no clear zone as in lepromatous leprosy, but that the infiltrate extends to and erodes the basal layer of the epidermis. X84, AFIP 72-12465.

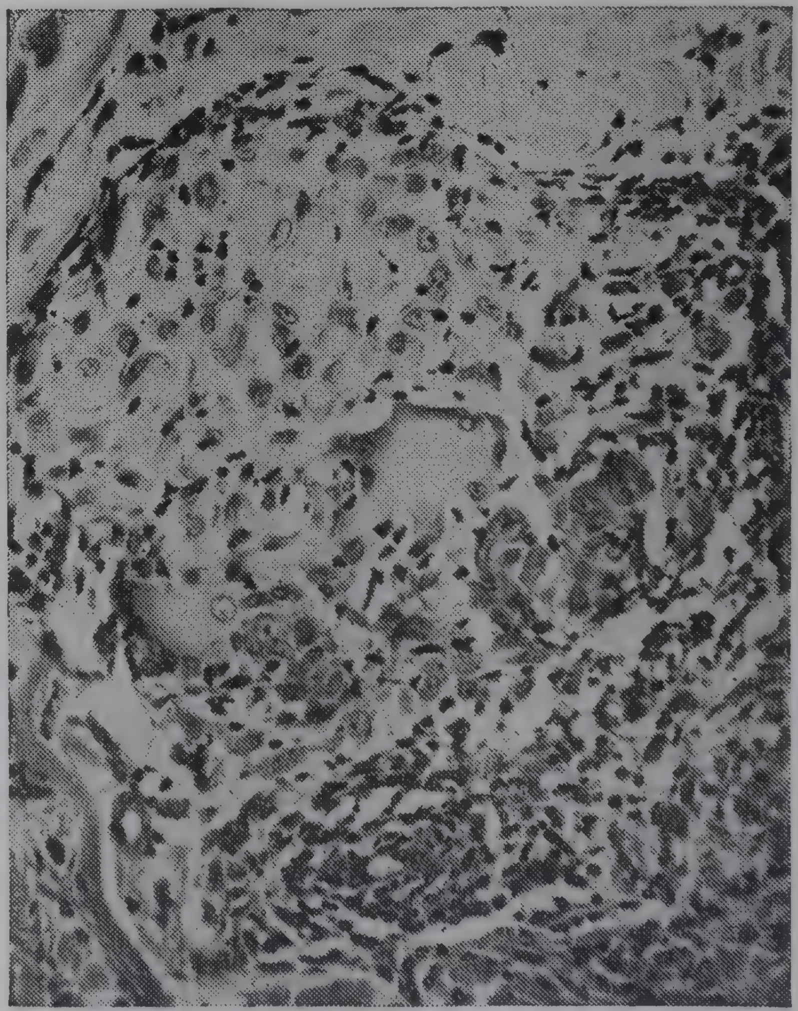


Fig. 29. Tuberculoid leprosy. This epithelioid cell granuloma in the skin suggests sarcoidosis. X(approx.) 225, AFIP 74-12821-2.

bacilli. Bacilli are sparse or numerous, depending respectively on the predominance of the tuberculoid or the lepromatous features. Accurate classification of the disease in patients with borderline leprosy is essential because in these patients chemotherapy must be used judiciously to lessen the risk of neuritis.

Fig. 30A. Borderline leprosy. Plaques and ring lesions suddenly developed in this Filipino patient about 3 weeks before this picture was taken. He had fever, and several peripheral nerves were tender and painful. AFIP 74-8485-2.

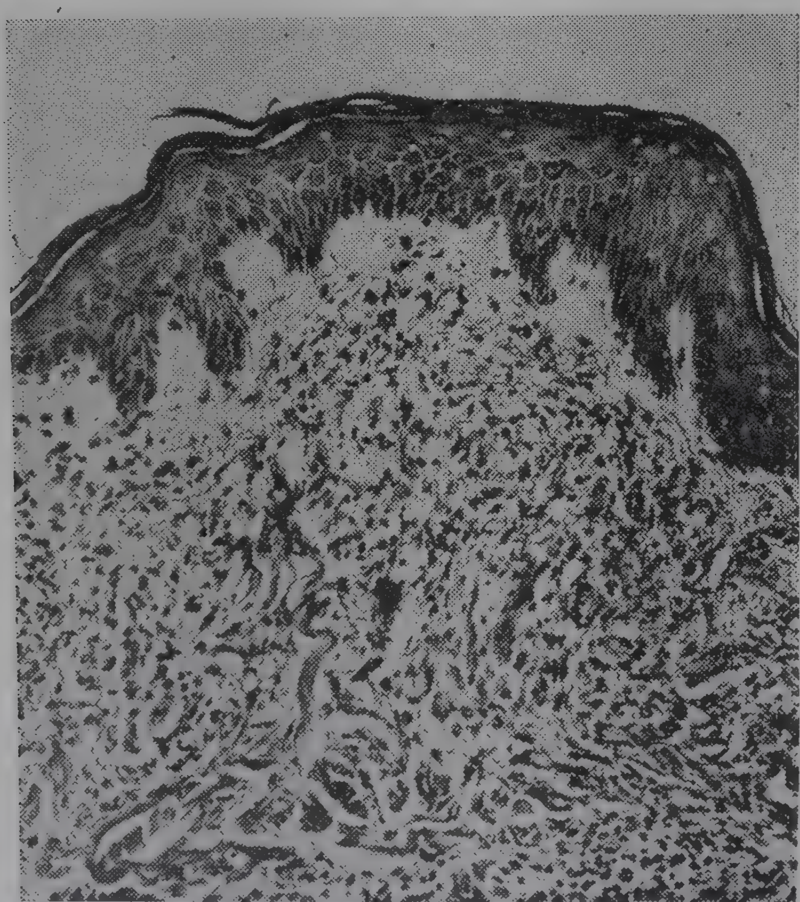


Fig. 30B. Borderline leprosy. Biopsy from margin of a ring lesion of patient shown in Fig. 30A. There is no clear zone as in lepromatous leprosy. The infiltrate is neither clearly tuberculoid nor lepromatous. Bacilli were few. X145, AFIP 74-3143.

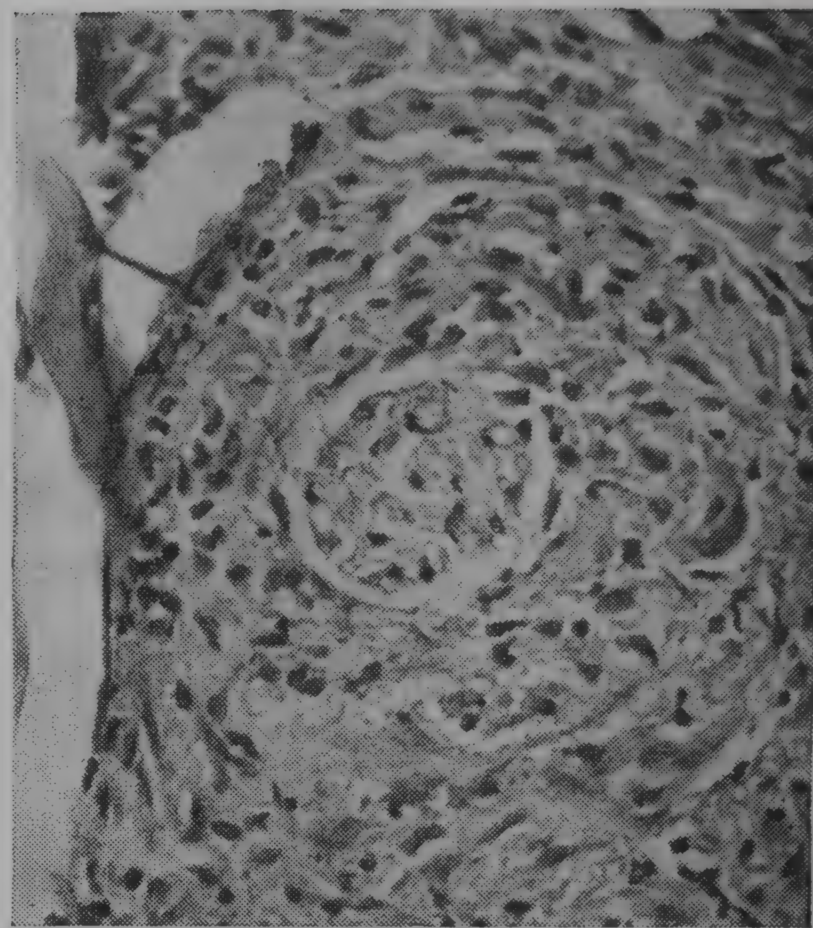


Fig. 30C. Borderline leprosy. Another area of section shown in Fig. 30B. Cells are somewhat suggestive of epithelioid type. The nerve shows very little histologic change. X530, AFIP 74-3145.

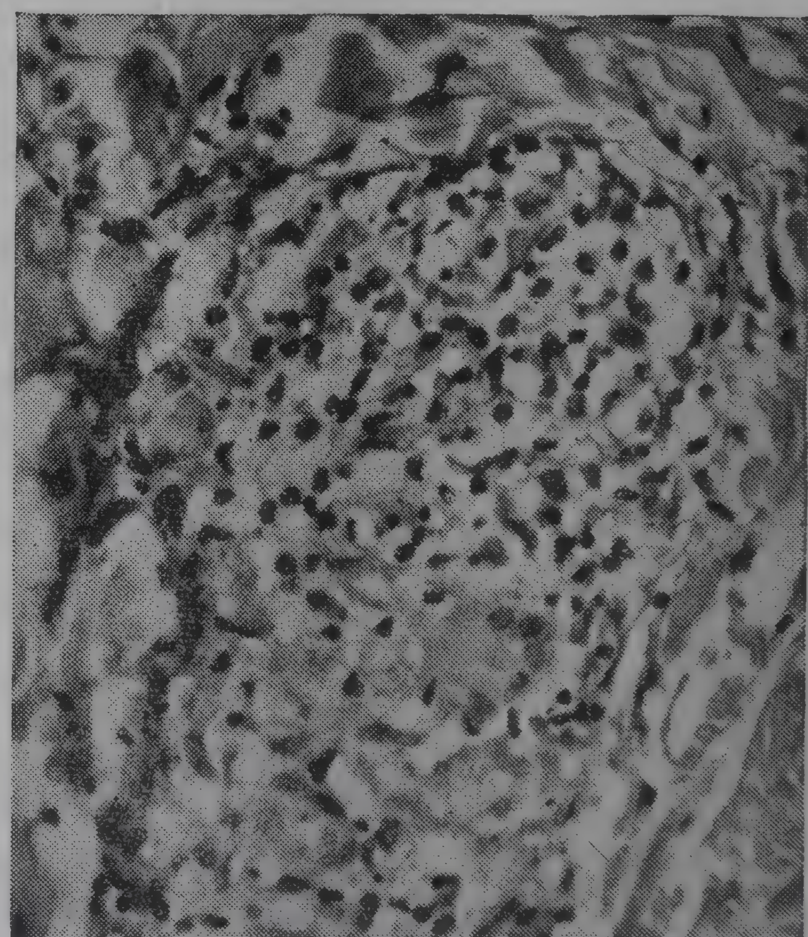


Fig. 31. Borderline leprosy, midzone, with more tuberculoid features than shown in preceding illustrations. Observe a partly developed epithelioid cell granuloma. Nerves in this section showed mild round cell infiltrate and many phagocytes with bacilli. X440, AFIP 72-12458.

In **indeterminate leprosy,** the histopathologist may be able to diagnose only mild, nonspecific, chronic dermatitis. There may be minimal round cell infiltration about small blood vessels or appendages. All small nerves should be searched thoroughly for bacilli, even though there is no obvious intraneural inflammatory reaction. In these early lesions, a few bacilli may be in the infiltrate or within the fibers of smooth muscle. A histopathologic diagnosis of indeterminate leprosy cannot be made without demonstrating bacilli.

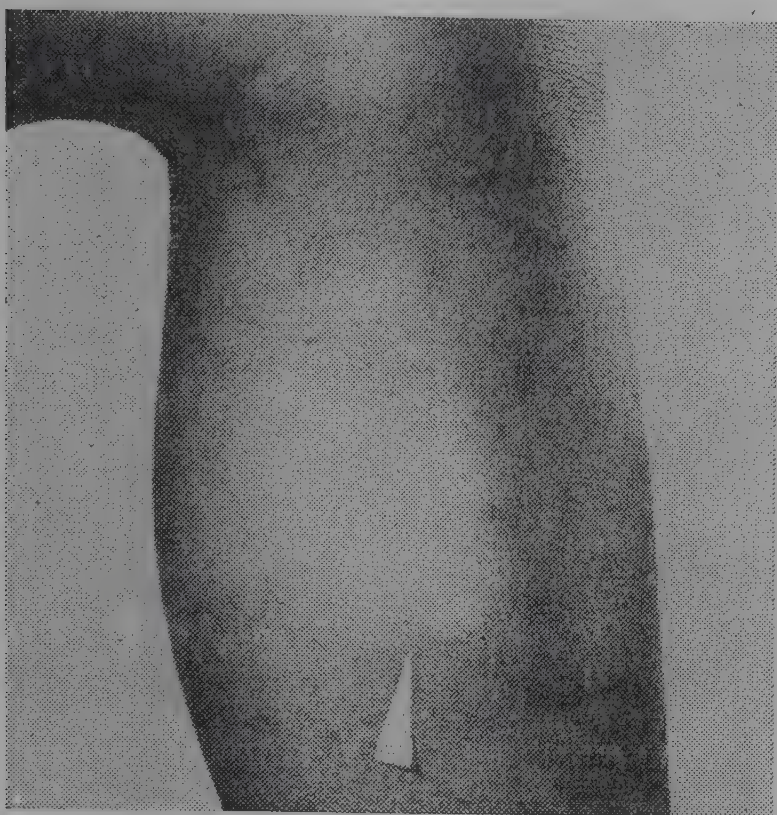
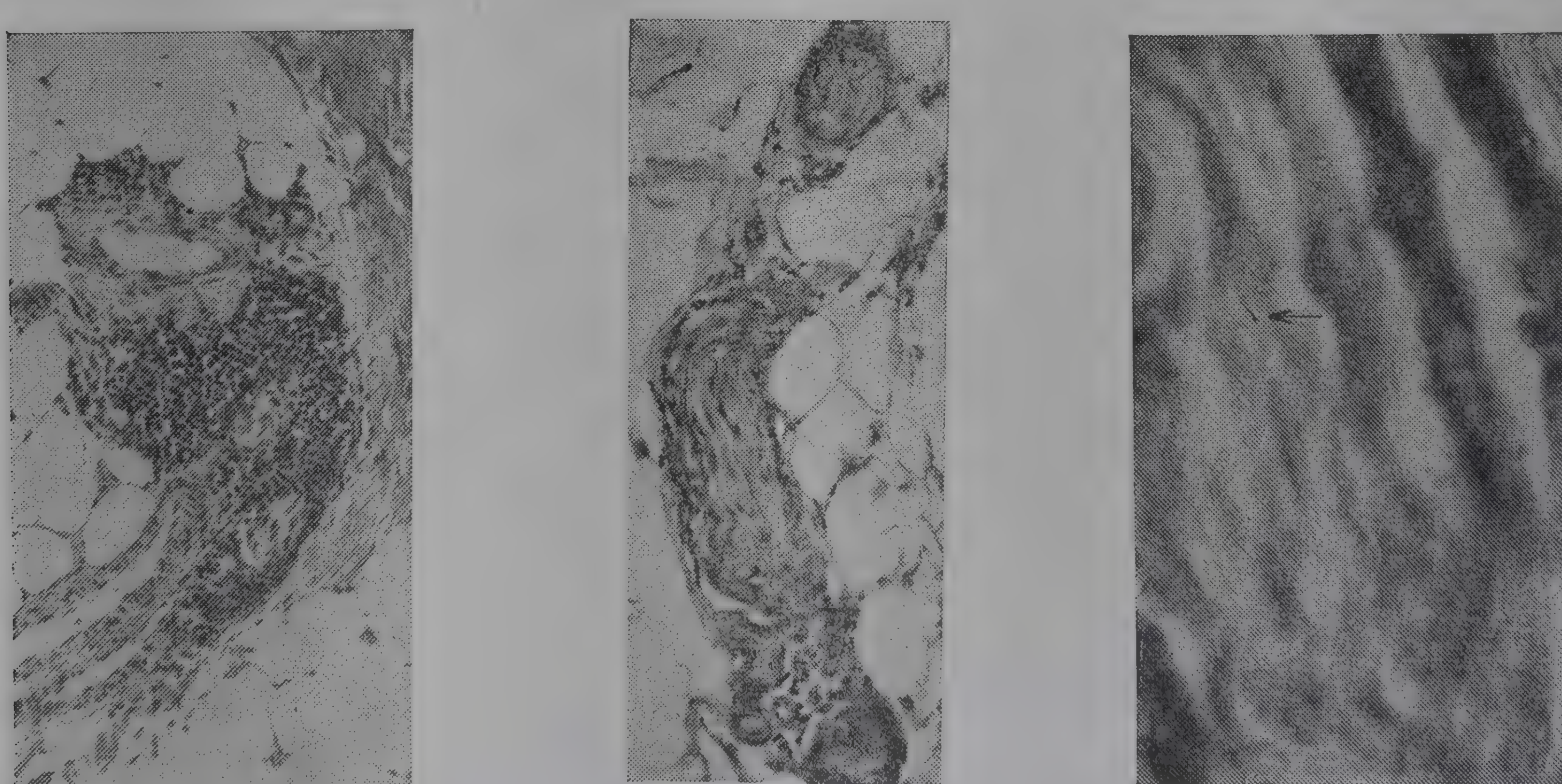


Fig. 32. Lesion of indeterminate leprosy, leg of Filipino patient. The lesion now is flat and hypopigmented. Earlier, it was probably erythematous. AFIP 74-9029-1.

Fig. 33. Indeterminate leprosy. There is a mild, round cell infiltrate. Unless bacilli are seen in nerves, the lesion can only be diagnosed as chronic dermatitis (see Fig. 34C). ×80, AFIP 75-2627.



A B C

Fig. 34. **A.** A nerve in section shown in Fig. 33. There is dense lymphocytic infiltrate around an intact nerve. X195, AFIP 72-12486. **B.** Another intact nerve from the same section shows only a few perineural round cells. X130, AFIP 75-2626. **C.** The nerve shown in **B** contained a few acidfast bacilli. One is shown (*arrow*). Therefore, the lesion can be diagnosed histopathologically as indeterminate leprosy. X1260, AFIP 72-12469.

As previously stated, the gross appearance of "**histoid" lepromatous leprosy** resembles dermatofibroma or neurofibroma. Microscopically also, the typical histoid nodule has whorls and fascicles of spindle cells. These spindle cells, however, contain numerous well preserved acid-fast bacilli arranged parallel to the long axis of the cells.

Nerve Involvement. *M. leprae*, in our experience at the AFIP, is the only *Mycobacterium* that regularly invades nerves. Nerves are involved in all types of leprosy. In many patients, the large nerves closest to the surface of the skin such as the ulnar near the elbow or the great auricular of the neck are visibly and palpably enlarged.

In lepromatous leprosy, macrophages and Schwann cells within nerves contain bacilli, and the increasing numbers of infected cells may eventually enlarge the fascicles and destroy nerve fibers.

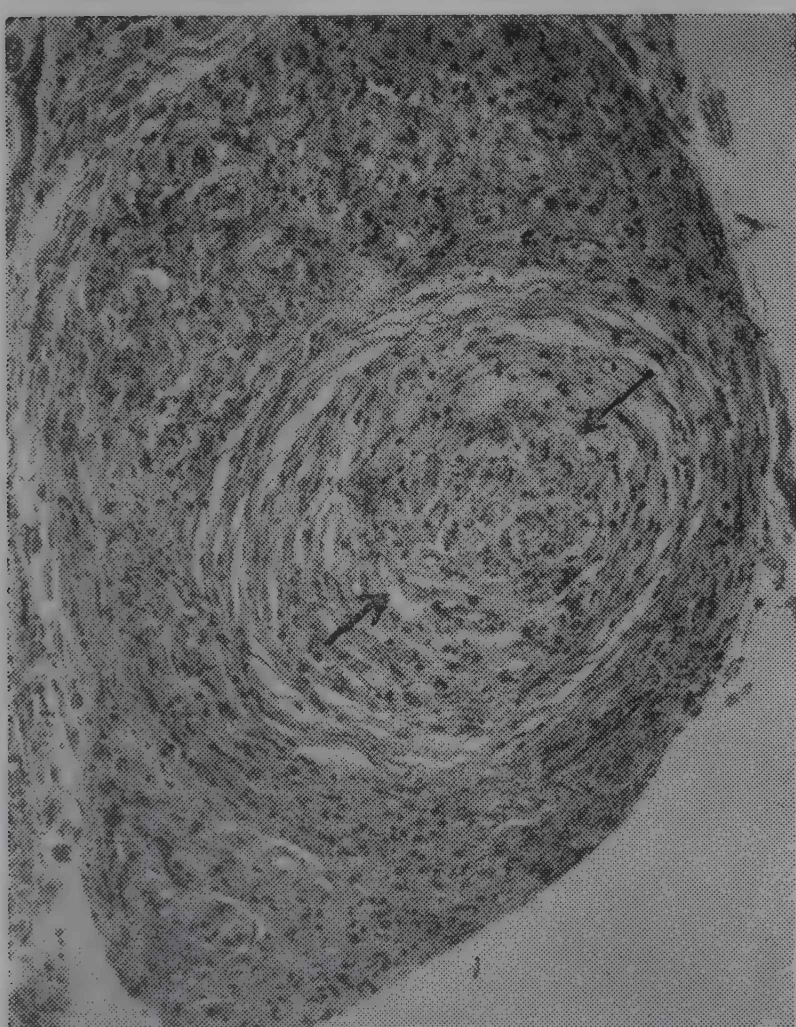


Fig. 35. Nerve lepromatous leprosy. The nerve (*between arrows*) has not been destroyed, but is being constricted by the encircling concentric collar of spindle cells. In the Fite-Faraco, acid-fast stain there were numerous bacilli in the nerve, in the spindle cells of the constricting collar, and in the surrounding lepromatous infiltrate. X200, AFIP 59-5945.

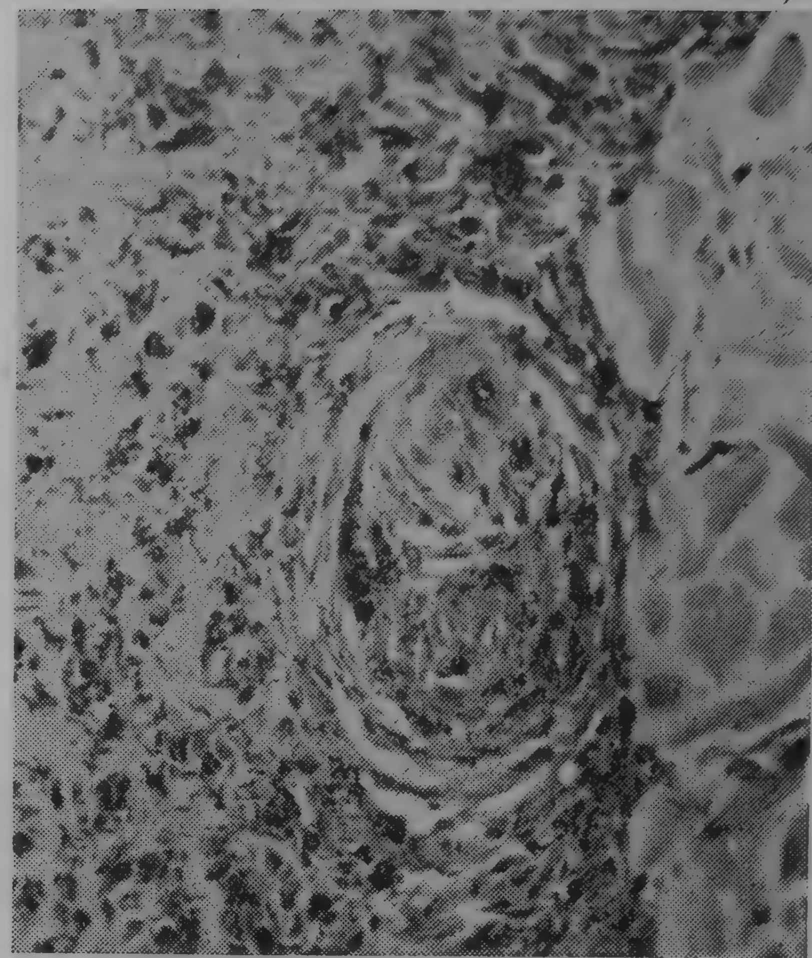


Fig. 36. Nerve lepromatous leprosy,. Numerous bacilli, extracellular or in phagocytes within the nerve, but no cellular infiltrate. Outside the nerve are numerous macrophages crowded with bacilli. Fite-Faraco, X350, AFIP 73-7532.

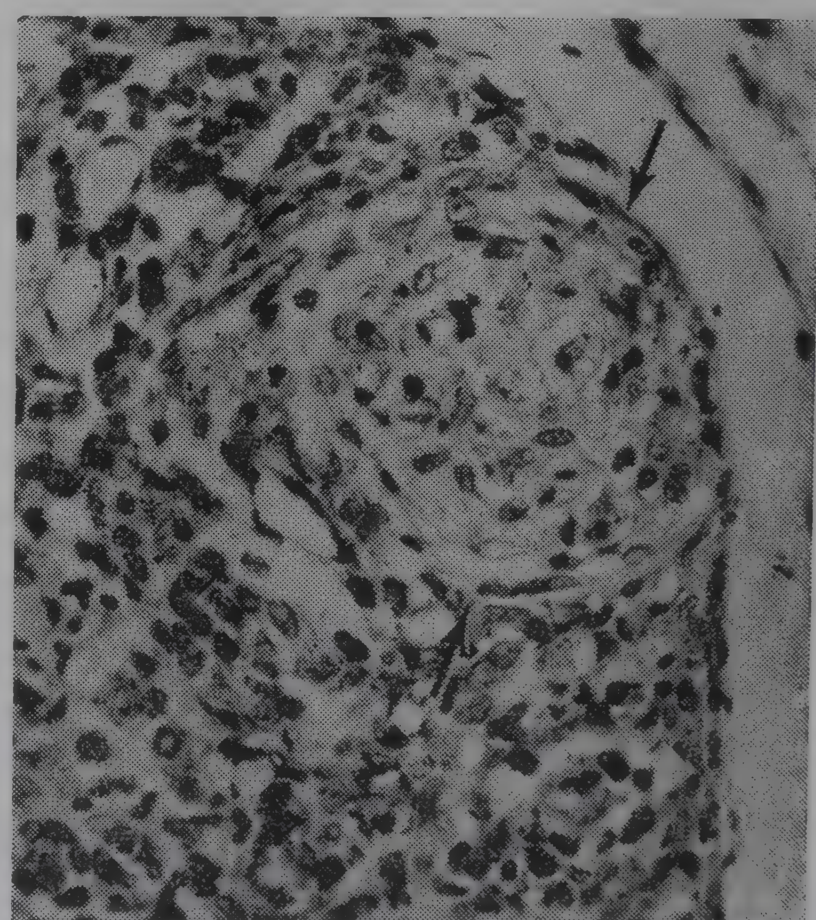
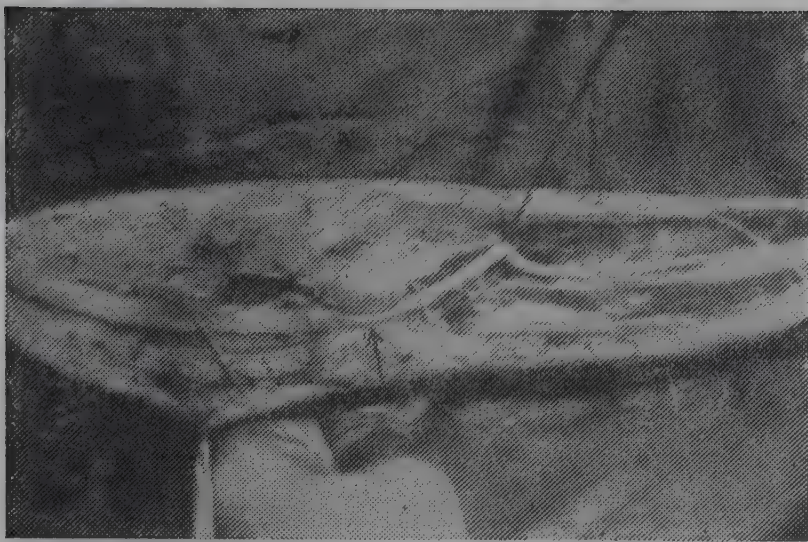


Fig. 37. Cross-section of nerve (*between arrows*) lepromatous leprosy. Numerous bacilli, many appearing as black intracellular masses. Fite-Faraco, X418, AFIP 54-18771.



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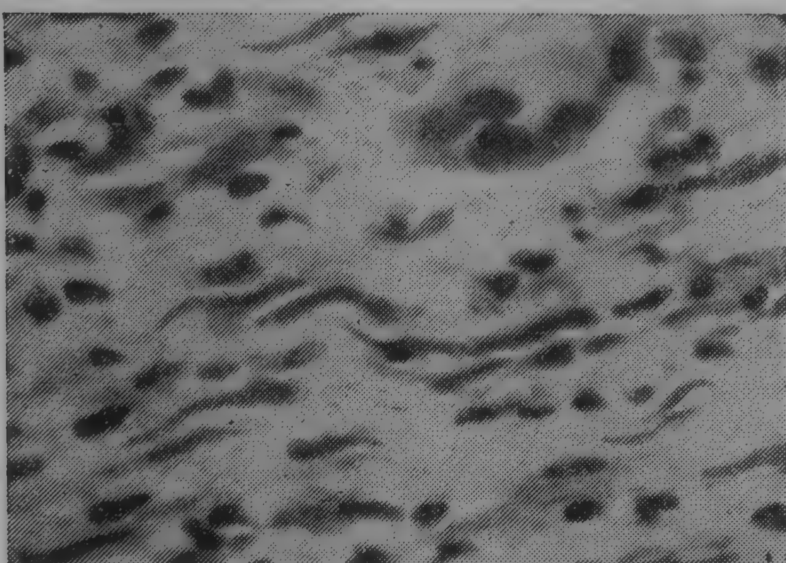


B

Fig. 38. **A.** Surgical exposure of enlarged ulnar nerve in patient with painful neuritis caused by borderline leprosy. The nerve is compressed in the olecranon groove (*arrow*) and greatly swollen above that level. There is less swelling of the nerve in the forearm. AFIP 75-12233. **B.** Histopathologically, there are numerous irregular Schwann cells, round cells, an occasional Langhans giant cell, and a few clusters of *M. leprae*. X(approx.)300, AFIP 75-15605. (Courtesy of Drs. N. H. Antia and D. K. Dastur. J. J. Group of Hospitals, Bombay, India.)

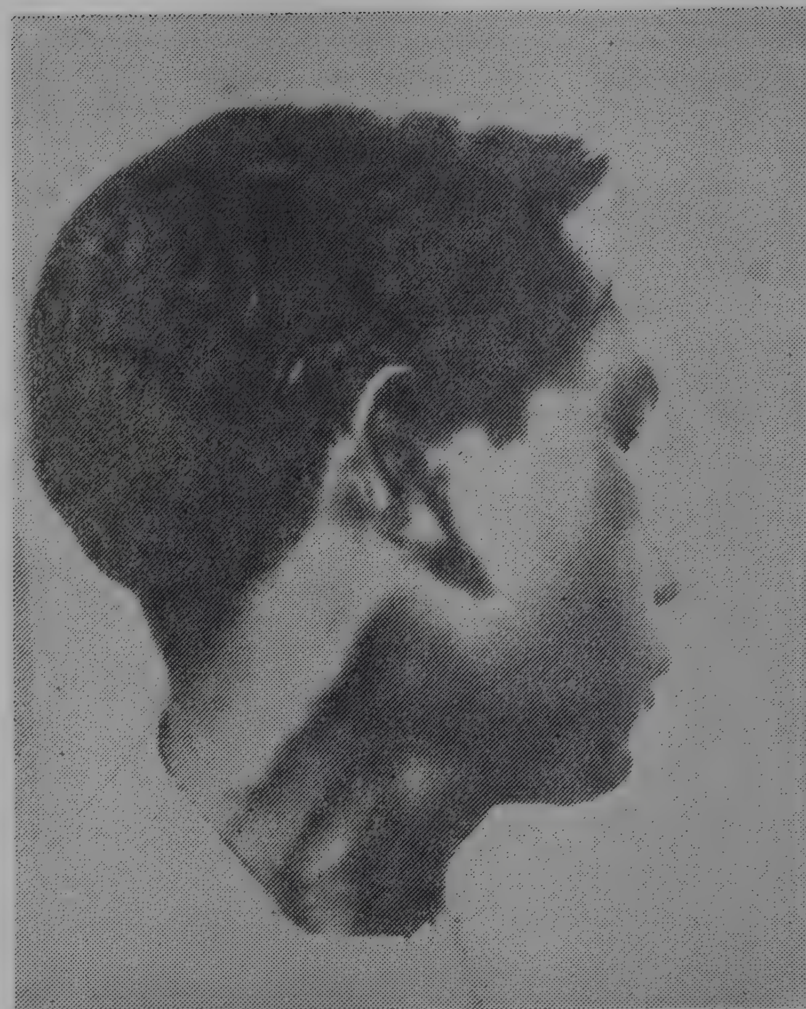


Fig. 39A. Tuberculoid or near tuberculoid leprosy. Enlargement, great auricular nerve. AFIP 75-15877.

Fig. 39B. Tuberculoid leprosy. Dermal nerve completely destroyed by an epithelioid cell granulomatous process. X130, AFIP 65-1641.

In tuberculoid or borderline-tuberculoid leprosy, even though bacilli are few, the proliferation of epithelioid cells and mononuclear cells enlarges nerve bundles and may totally destroy the nerve fibers. During reactions, increased cellularity and edema may rapidly and severely damage nerves, causing pain, paresis, and paralysis. In some patients, the only manifestation of leprosy may be the involvement of large peripheral nerves (pure neural leprosy). Muscular and sensory disturbances from damaged nerves lead to deformities that are largely responsible for the universal fear of leprosy. Nerve trunk infection may also alter autonomic nerve function and lead to concentric atrophy and eventual

Fig. 40. Considerably thickened supraorbital nerve (rt), edema of right side of the face particularly noticeable on the lips, and facial neuritis in a case of BT leprosy in reaction. (Photograph courtesy of Dr. B. R. Chatterjee)

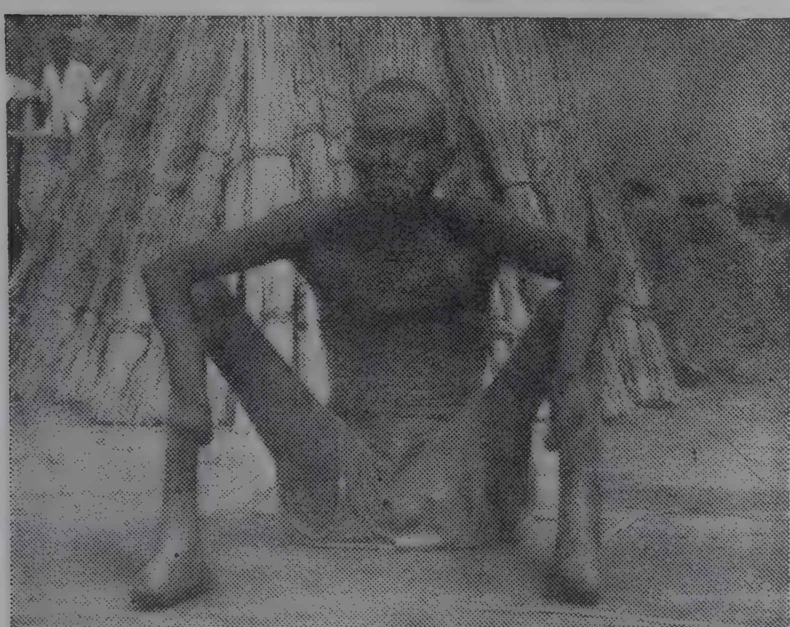
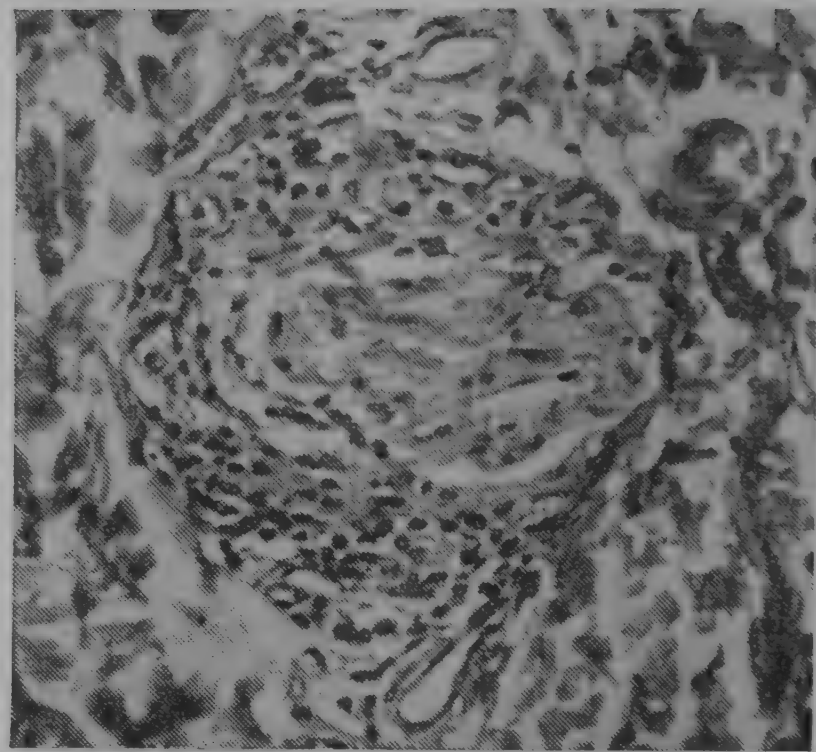


Fig. 41. Severe hand and foot deformity in borderline leprosy. The digits have been completely lost as a result of trauma and infection in anesthetic hands and feet. Impaired motor function also contributed to this damage. AFIP 69-3567.



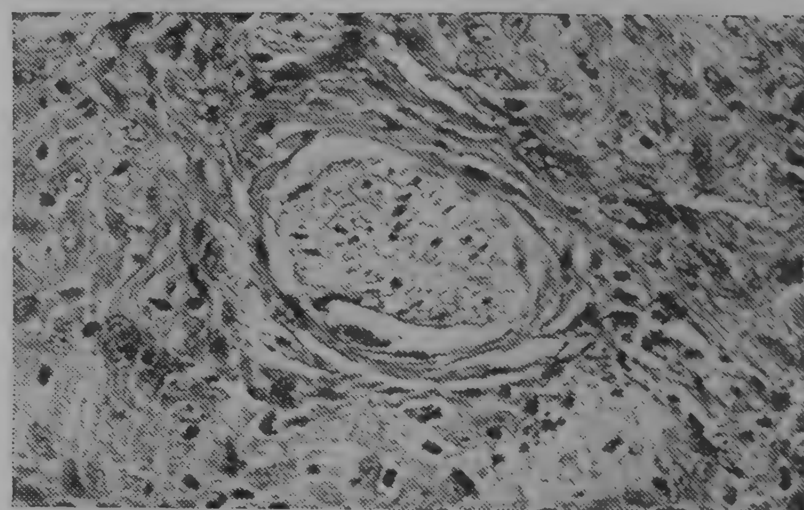


Fig. 42. *Upper* : Beginning involvement of a small dermal nerve in a lesion of tuberculoid leprosy. The perineurium has been destroyed by the epithelioid cell infiltrate, and within nerve, there is an increase in Schwann cells and round cells. X330, AFIP 60-6262. *Lower* : Nerve in sarcoid lesion of skin. Although enveloped by the epithelioid cell granuloma, the nerve is entirely normal. X (approx.) 300, AFIP 54-19598.

Fig. 43. Tuberculoid leprosy. Abscess of radial nerve at wrist in an adult Zairian man. AFIP 75-15596.

absorption of phalanges. Occasionally, the end result of tuberculoid or near tuberculoid leprosy in a large nerve may be a caseous abscess. Abscesses of nerves have also been reported in patients with lepromatous leprosy but are rare.

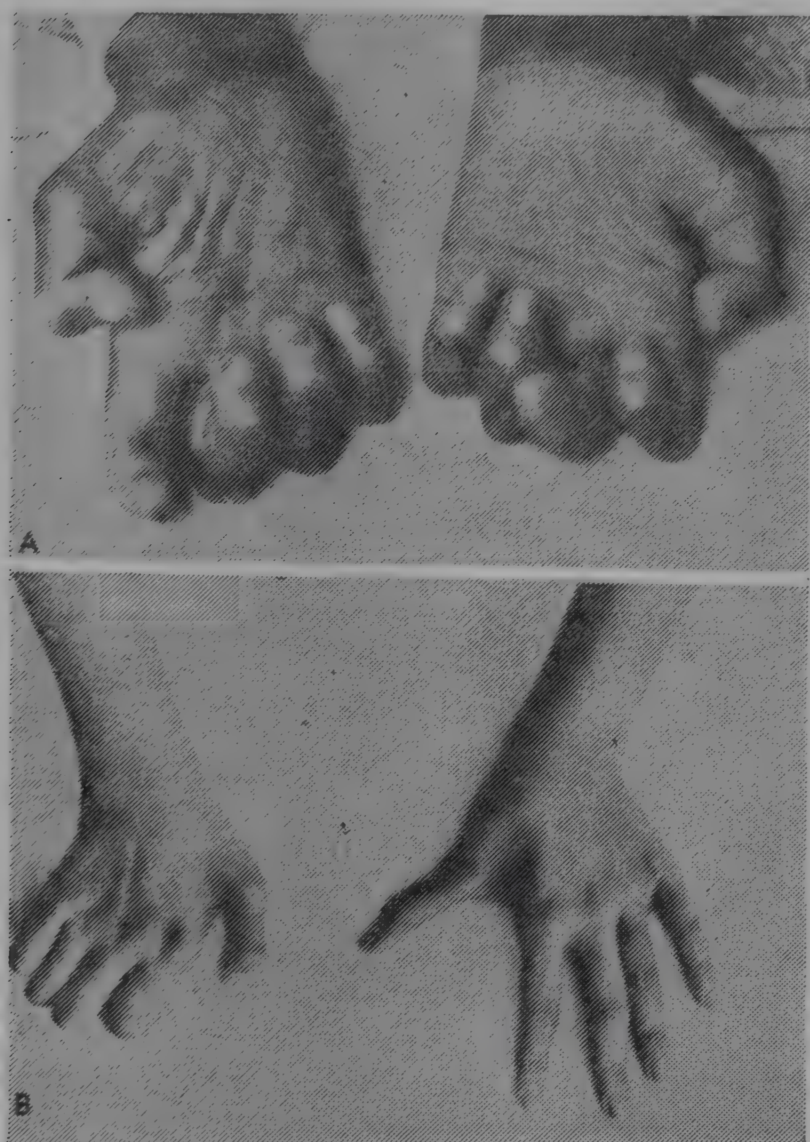
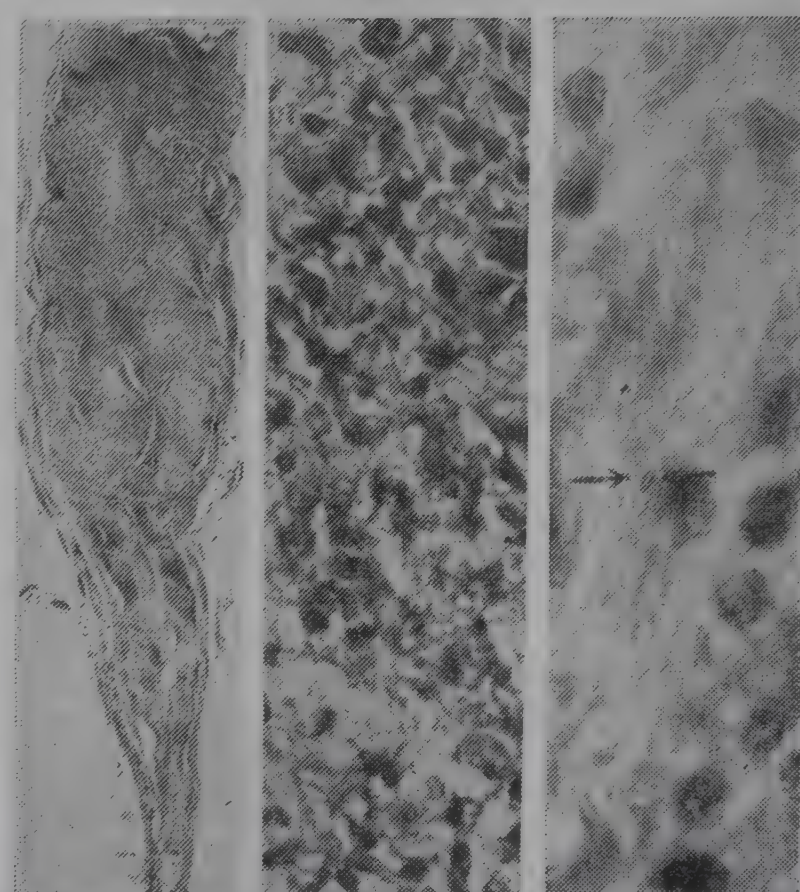


Fig. 44. **A.** Clawing deformity of hands in leprosy. The patient's right hand demonstrates clearly the atrophy of thenar and hypothenar muscles. Note also dystrophy of some nails. Deformities of this type are seen in bacteriologically positive patients. **B.** Deformity due to nerve damage which may be seen in bacteriologically negative patients. There is clawing and muscle atrophy. **A & B.** AFIP 75-15807.

Temperature Selectivity. A distinct feature of leprosy is the distribution of lesions in the cooler parts of the body—prominences of the skin, mucous membranes of the upper respiratory tract (especially the turbinates, nasal septum, and larynx), anterior part of the eye, testis, lymph nodes draining dermal lesions, and nerve trunks that are near the surface of the skin. The testis is involved in moderately advanced or advanced leprosy. The temperature of the descended testis is several degrees cooler than abdominal organs. In untreated lepromatous patients, severe lesions causing impairment of vision or blindness may develop in the cornea, iris, and ciliary body, locations where the temperature is several degrees cooler than in the posterior segment of the eye.

Leprosy bacilli are readily demonstrated in the blood of patients with advanced lepromatous leprosy; the reticuloendothelial cells of liver and spleen phagocytose circulating bacilli and thus microscopic aggregates of lepra cells develop in these organs. These aggregates are rarely large enough to be seen macroscopically. Although in exacerbations of untreated lepromatous leprosy macrophages containing bacilli may be in any organ, in man, established progressive lesions of lung, gastrointestinal tract, brain, and spinal cord have not been demonstrated in the cases filed at the AFIP.



A B C

Fig. 45. **A.** Longitudinal section through "tumor" radial nerve at wrist of a physician from Asia. The small end shows the size of the uninfected nerve. No other nerve of skin lesions were found in this patient. X6.5, AFIP 67-2672. (Case courtesy of Dr. K. R. Grim, Durham, N. C.) **B.** The type of epithelioid cell granuloma that composed the major part of the "tumor." No bacilli are seen in the granuloma. X440, AFIP 66-5842. **C.** Area of partly preserved nerve at a point adjacent to the granuloma. Between arrows are two well stained bacilli which were the only bacilli found during a 1 hour search. Fite-Faraco, X1080, AFIP 67-2677.

Lymph Node Involvement. In lymph nodes that drain cutaneous lesions of patients with lepromatous and near lepromatous leprosy, the cells of the paracortical zones may be partly or almost totally replaced by large macrophages filled with bacilli. In tuberculoid leprosy, granulomas comprised of epithelioid cells may develop in lymph nodes.

Fig. 46. Dermal nerve in tuberculoid leprosy has been almost destroyed by epithelioid cell and lymphocytic infiltrate. Remnants of nerves seen above X145, AFIP 60-6261.

Fig. 47. **A.** Tumor of a testis discovered during discharge examination of a soldier. X4, AFIP 64-5530.

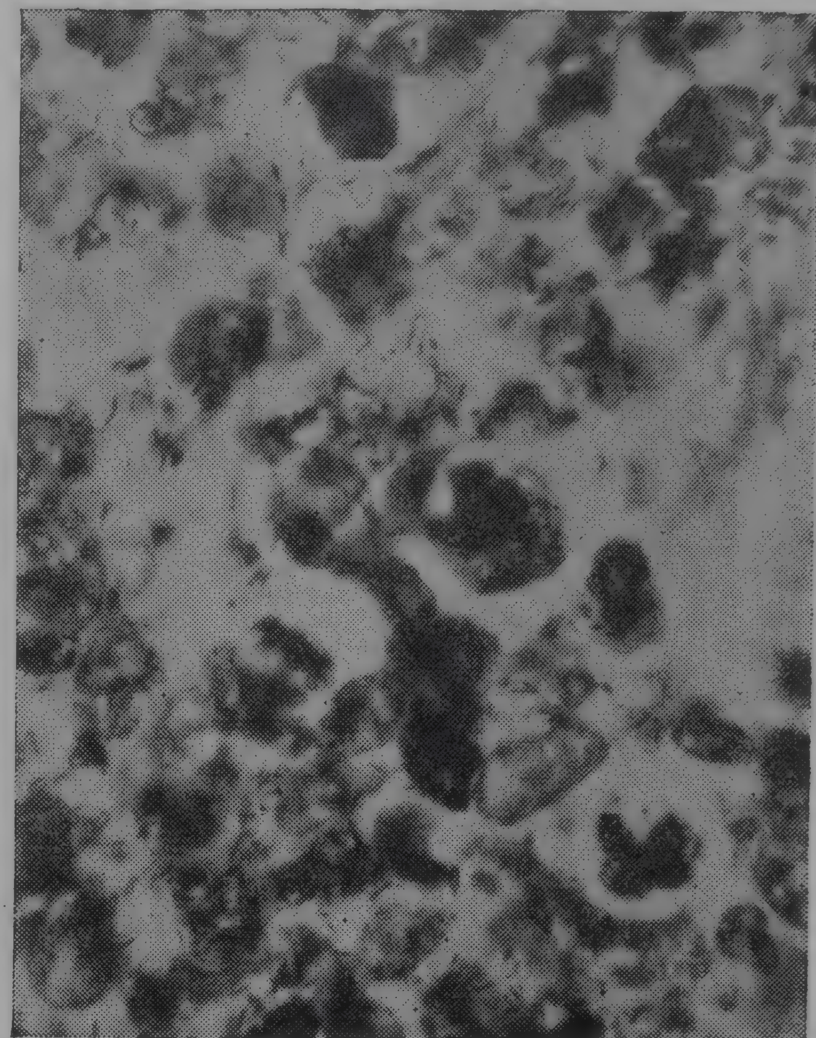


Fig. 47. **B.** At higher power a Fite-Faraco stained section showed numerous *M. leprae* in phagocytes. The black structures in histiocytes are masses of bacilli. Examination of the patient by a leprologist revealed disseminated lepromatous leprosy that had not been recognized during his military service. Fite-Faraco, X1200, AFIP 66-13124. (This histopathologic diagnosis was made by the late Dr. Arnold Strauss, Norfolk, Va.)

Fig. 48. Lepromatous leprosy. There is a leproma (*arrows*) in the perilimbal area, and infiltrations of the lid with loss of lashes on the upper lid in this adult Zairian man. Lepromas in the eye were seen frequently during the presulfone era. AFIP 75-15591.

Control. By inoculating foot pads of mice with suspensions of *M. leprae* (obtained by biopsy of a lesion in a patient with lepromatous leprosy), Shepard has determined that after a few days of treatment with rifampin and 3 or 4 months with dapsone (DDS), the viability of the patient's bacilli cannot be

Fig. 49. **A.** Lepromatous leprosy, cornea. This photo-micrograph demonstrates serious involvement of the cornea by leprotic infiltrates. The black masses are leprosy bacilli. In the presulfone era, blindness was frequent in patients with advanced lepromatous leprosy. Fite-Faraco, X365, AFIP 59-5888.

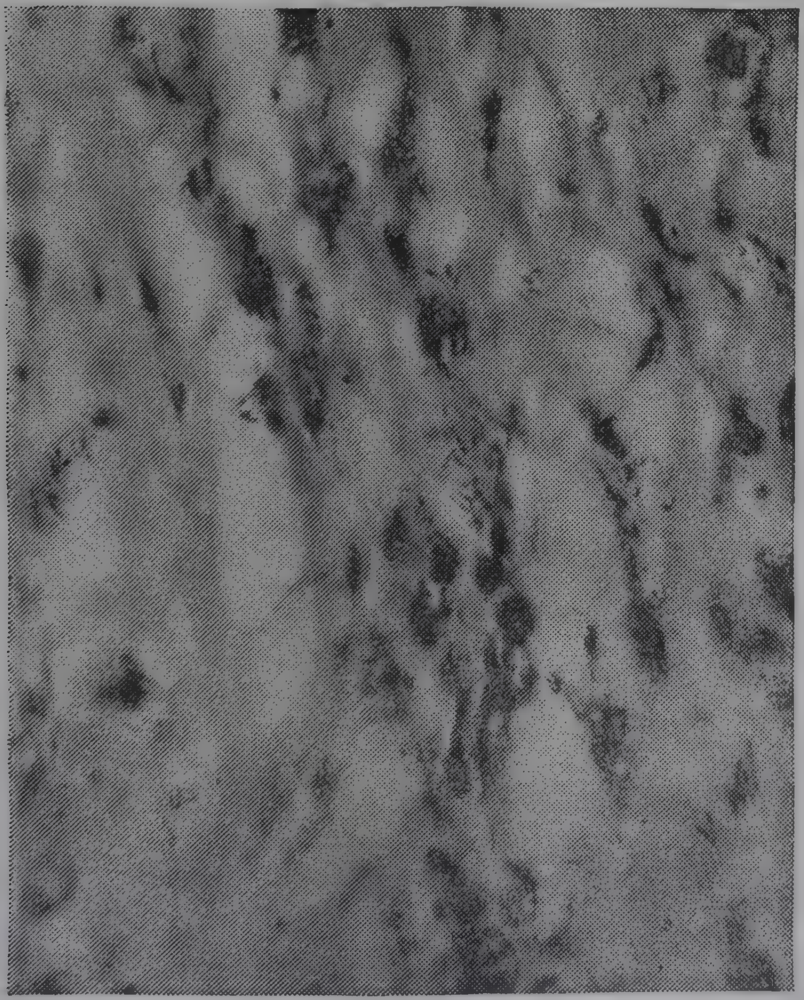


Fig. 49. **B.** Higher magnification of the lesion of cornea shown in Fig. 49A. Fite-Faraco, X1000, AFIP 59-5885.

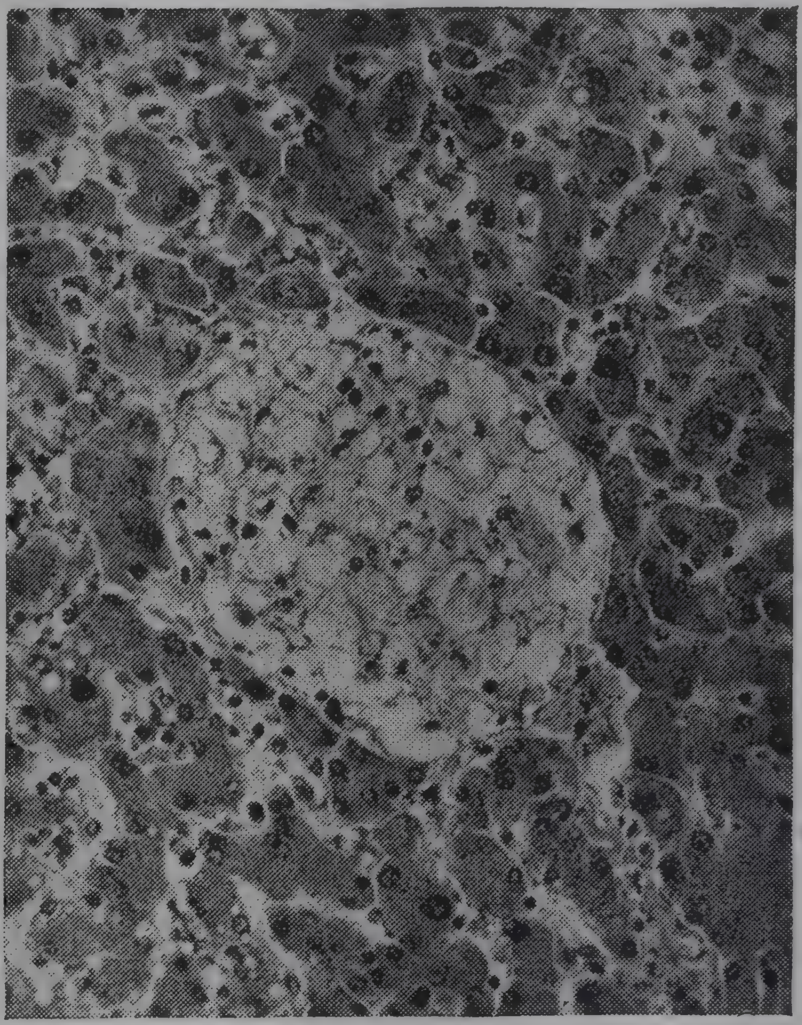


Fig. 50. Liver. Small aggregates of lepra cells and infected Kupffer cells are characteristic of advanced lepromatous leprosy. This patient had been treated; therefore, the infiltrate is degenerating. Bacilli were few. X340, AFIP 59-1145.

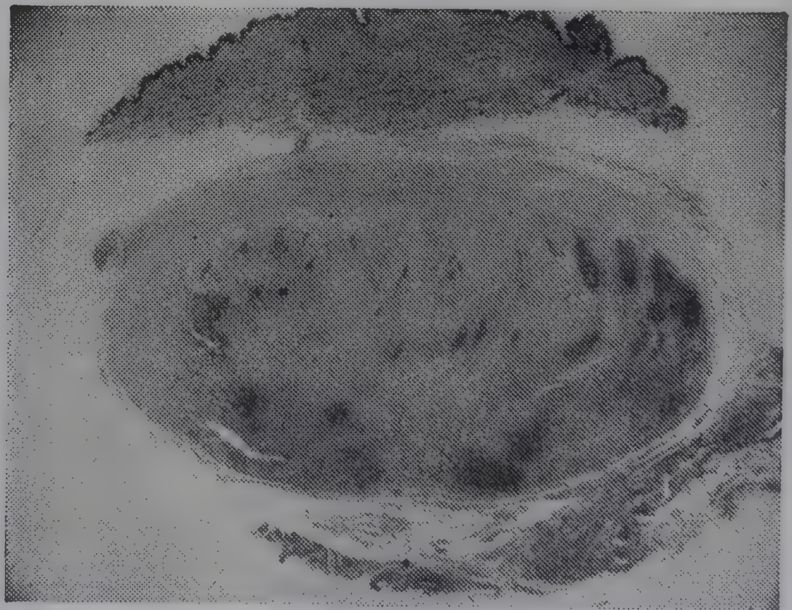


Fig. 51. Small subcutaneous node from the forearm of the same patient in Fig. 52 shows almost total replacement by lepra cells. X7.5, AFIP 72-12502.

Fig. 52. Lepromatous leprosy, lymph node. Foamy macrophages which contained many *M. leprae* are conspicuous in the parafollicular and medullary areas. Some are in lymphatic sinuses. X90, AFIP 72-12505.

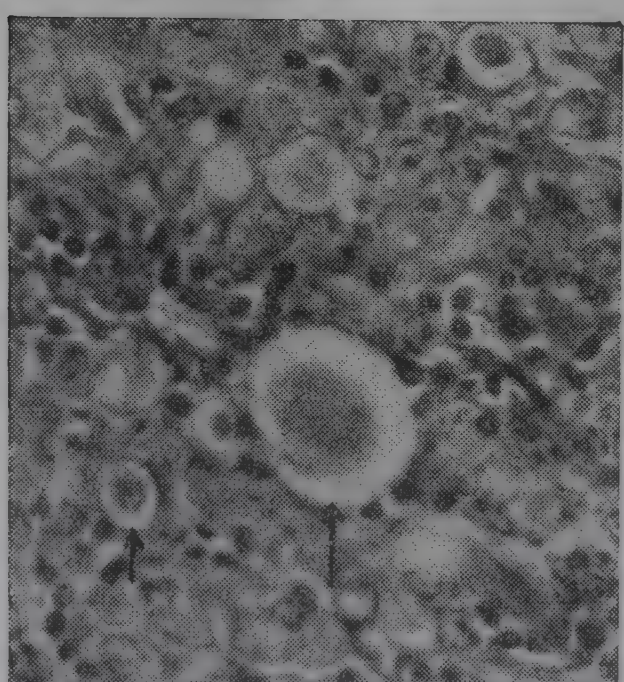


Fig. 53. In an H & E stained section of Fig. 51, the foamy macrophages (lepra cells) are well demonstrated. The arrows point to hematoxylin positive globular masses in clear spaces. X645, AFIP 72-12508.

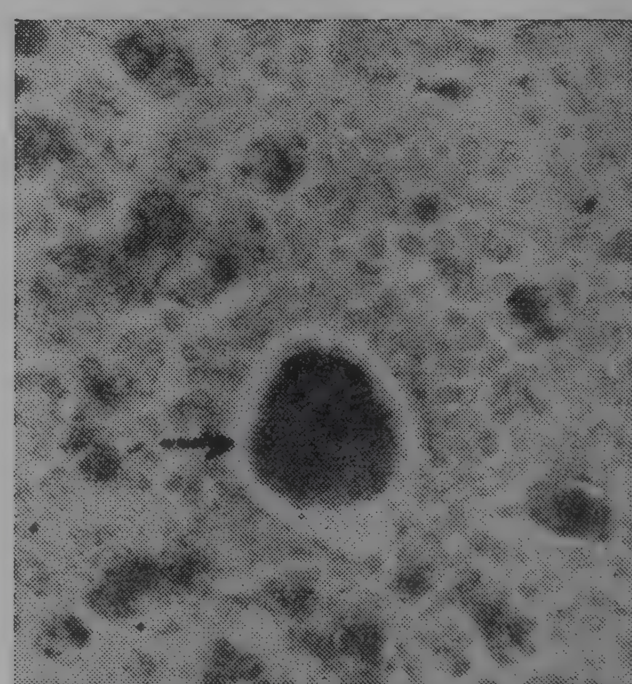


Fig. 54. Fite-Faraco stain of a replicate section of Fig. 53 shows acid-fast bacilli in lepra cells and in a large globus (*arrow*). X645, AFIP 72-12509.

demonstrated in mice. By the time a diagnosis is made in a patient with moderately advanced or advanced lepromatous leprosy, members of his family and other contacts have been exposed for many months. Thus, the prevailing practice by public health and leprosy control officers is to allow patients receiving an effective drug to remain with his family and continue normal social contacts.

BCG vaccination will convert many lepromin-negative individuals to positivity. In the hope that this vaccination would enhance cell-mediated immunity to leprosy, several large field studies have been undertaken. Unfortunately, the results have been variable and no conclusion on its effectiveness can be drawn.

Amyloidosis Complicating Leprosy. At U.S. Public Health Service Hospital in Carville, Louisiana, amyloid nephrosis was the declared cause of death in many patients with long-standing lepromatous leprosy.

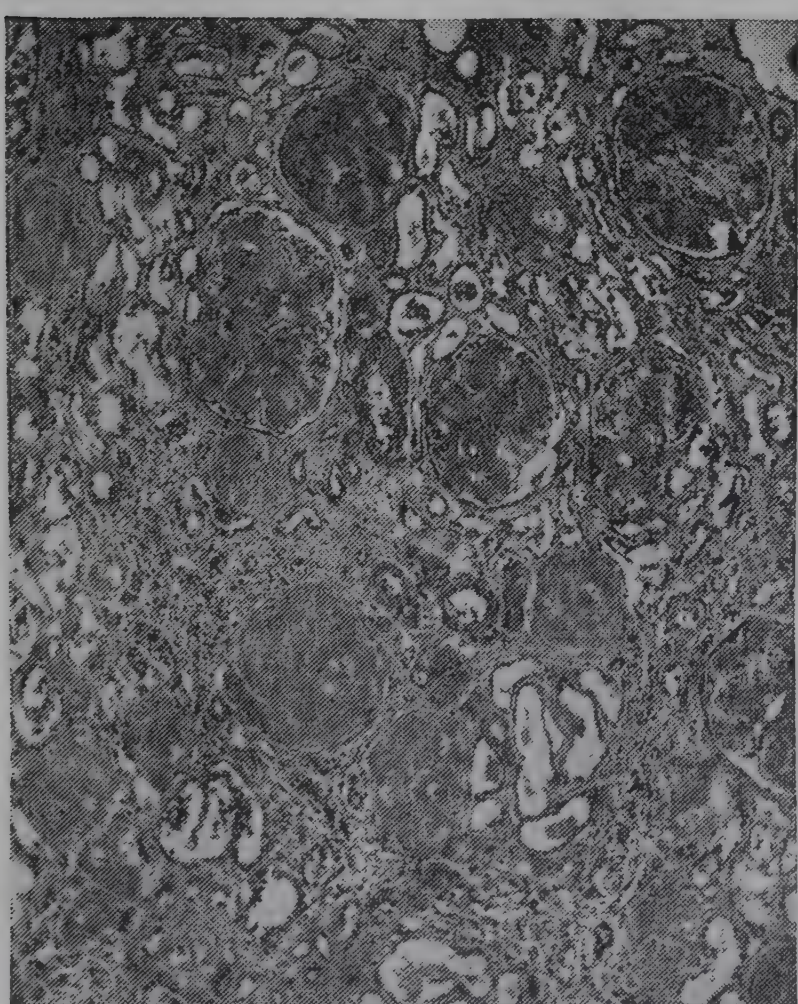


Fig. 55. Kidney. Amyloid in glomeruli and in some interstitial tissue. In former years, amyloid nephrosis was seen in approximately 40% of lepromatous patients at the USPHS Hospital, Carville, La. X34, AFIP 54-18445.

Spleens and livers of the patients also frequently contained amyloid. In leprosy hospitals in other parts of the world, amyloidosis is less prevalent.

Laboratory Diagnosis. Other than demonstrating acid-fast bacilli in smears made of tissue fluids and cells (obtained by slitting the skin with a scalpel or razor blade), there is no established clinical laboratory test for leprosy. A clinical diagnosis should be confirmed by histopathologic examination, if practical. In nonendemic areas, biopsy examination should be done for medico-legal documentation, even in patients with advanced disease.

The fear of leprosy, irrespective of geographic location or race, is so deeply ingrained that a diagnosis of leprosy even in its mildest form may stigmatize a patient to such a degree that he can never again lead a normal life in his community. Thus a histopathologist uncertain of the diagnosis or inexperienced in leprosy should obtain help from colleagues with experience. Diagnoses "compatible with" or "consistent with" leprosy should not be made to avoid the stigmatizing potential of such a diagnosis for a person without leprosy and also to prevent possible malpractice action.

Differential Diagnosis. The diagnosis of leprosy is sometimes difficult and must always depend on specific criteria, e.g., sensory changes, enlargement of nerves, presence of acid-fast bacilli, or typical histopathologic features. A mistaken diagnosis of leprosy can be disastrous and should be assiduously avoided by the clinician and histopathologist. Macular hypopigmented lesions of superficial fungi, nevi, vitiligo and filariasis are frequently misdiagnosed as leprosy. Some infiltrated lesions of the skin which may resemble leprosy are : mycoses, cutaneous leishmaniasis, psoriasis, lupus vulgaris, syphilis, lupus erythematosus, granuloma annulare, granuloma multiforme, neurofibromatosis, sarcoidosis, and lymphomatous infiltrates. Sometimes, peripheral neuropathies caused by avitaminosis, diabetes mellitus, syphilis, and lead toxicity can produce sensory or motor changes reminiscent of those caused by leprosy. Rarely, amyloidosis of nerves or a familial hypertrophic neuropathy causes enlarged and firm peripheral nerves which cannot be distinguished clinically from the neuropathy of leprosy. These lesions must be considered in patients suspected of having pure neural leprosy. Nasal involvement in

lepromatous leprosy can resemble lethal midline granuloma, Wegerer's granulomatosis or rhinoscleroma.

Sera from patients with moderately advanced and advanced lepromatous leprosy frequently give false positive reactions for syphilis, therefore, syphilis may be the first clinical diagnosis in a patient with leprosy.

Treatment. Diaminodiphenylsulfone (DDS), available in the United States of America as dapsone, is an effective, stable, inexpensive drug which has been used universally since the late 1940's in the treatment of leprosy. In most patients with lepromatous leprosy, continuous treatment must be given at least 4 or 5 years to achieve bacteriologic negativity. Many leprologists recommend life-time therapy to prevent relapse in patients with lepromatous leprosy. Other effective but much more costly drugs are clofazimine (Lamprene) and rifampin.

There have been a few attempts to enhance the resistance of patients with lepromatous leprosy by the use of transfer factor prepared from lepromin-positive individuals, but the results are as yet inconclusive.

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For a comprehensive coverage of all aspects of leprosy, the reader should consult the **International Journal of Leprory,** Vols. 1-44 (Business Office : 297 Park Ave., South, Room 40, New York, N. Y. 10003), **Leprosy Review**, Vols. 1-46. (Academic Press, 111 Fifth Ave., New York, N.Y. 10003), and the **Star,** published bimonthly by the patients of USPHS Hospital, Carville, La. 70721.

ACKNOWLEDGEMENT

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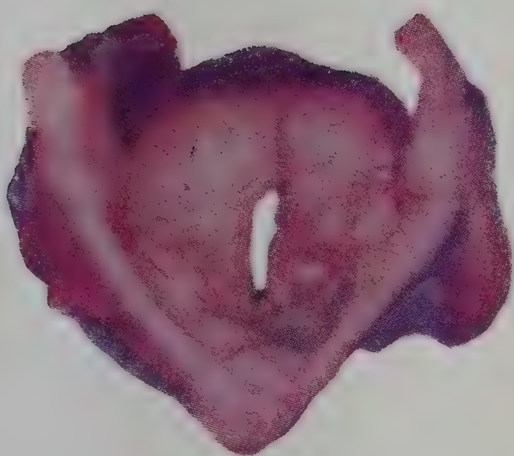
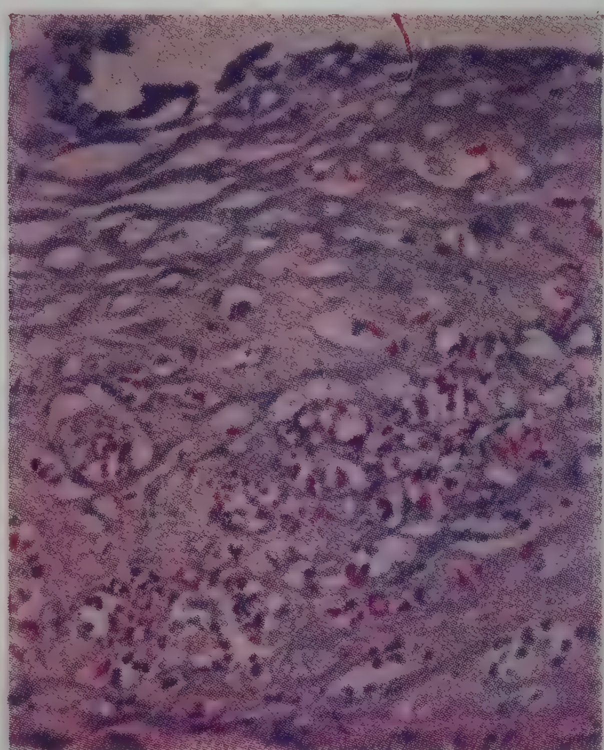
Fig 1. Diffuse lepromatous leprosy in a Nepalese twin, generally difficult of diagnosis. The red spot on the forehead was for differentiating the twins. (Photograph courtesy of Dr. B. R. Chatterjee).

Fig. 2 A real 'claw' hand in a Bengalee patient. (Photograph courtesy of Dr. B. R. Chatterjee)

3. A new lesion in a patient who had many lesions of borderline leprosy. The patient, a veteran with service in the Far East in World War II, was treated for ringworm for several years until seen by a dermatologist with experience in leprosy. AFIP 57-16914-1.



. Larynx showing obliteration of ocal cords and stenosis caused by epromatous leprosy. Before the sulfone rugs were used in leprosaria, at least 0% of lepromatous patients required racheostomies because of laryngeal tenosis. AFIP 74-9025-5.



5. Section through lesion of larynx shown at left. Fite-Faraco, X155, AFIP 54-19170,

6. Iridocyclitis and conjunctivitis in patient with lepromatous leprosy. AFIP 75-14043. (Courtesy of Dr. Rolla Wolcott, formerly at USPHS Hospital, Carville, La.)

7. Erythema nodosum leprosum (ENL) in Filipino woman with lepromatous leprosy. Observe the numerous red papulonodules ; some nodules with softened centers will rupture and discharge purulent exudate. AFIP 74-9029-7.

8. Lucio leprosy in a patient of Mexican origin at USPHS Hospital in Carville, La. The triangular ulcers are the result of obliterative leprotic inflammation of small arteries. There was diffuse lepromatous involvement of the skin. AFIP 74-9029-6.

PATHOLOGY OF LEPROSY

C. K. JOB

INTRODUCTION

During the last decade considerable advances have been made in the study and understanding of leprosy which had been the cinderella of Medical Scientists. Leprosy is now regarded as an infectious disease whose causative organism is M. leprae. The main organs affected are the skin and the nerves. The disease has a variety of manifestations which depend mainly on the resistance of the infected individuals. Leprosy is prevalent thoughout the world, affects more men than women and is contracted at all age groups. How the organisms gain entry into the human system is still a debatable question and most probably it enters through the skin and mucous membrane. Fear and prejudice against the disease among lay public and medical men continue to be the main reasons for the slow progress in the control of the disease in the world to-day.

Since the manifestations of leprosy is so varied, a classification is essential. A classification which is simple and also based on clinical appearance, immunological status, bacteriological assessment and pathological changes is the best for it can be easily understood and used by most people working in leprosy.

The concept that leprosy begins with an early lesion which when matures falls into a spectrum is the basis in the classification given below

Classification of Leprosy

The tuberculoid and lepromatous types are at the poles and the spectral spread is represented by the borderline group. There are some especially in India who develop only nerve lesions and therefore are called purely neural leprosy patients. They may belong to any of the above forms depending on their immune response.

INDETERMINATE GROUP OF LEPROSY

Indeterminate leprosy is considered the earliest manifestation of the disease. There may be one or more hypopigmented macules and they are often present in the extremities, buttocks or face. Some lesions show loss of sensation but in many no sensory loss can be demonstrated.

Histologically the epidermis is normal. Focal collections of round cells are present throughout the corium specially distributed around skin appendages. The identification of the lesion as leprosy can be quite difficult because of the nonspecific nature and distribution of the inflammatory cells. But often the inflammatory response selectively affects the small cutaneous nerve bundles (fig. 1) and arrectores pilorum muscles. Acid fast stain may show bacilli inside nerve bundles and smooth muscle bundles. Only then diagnosis of indeterminate leprosy can be confirmed.

It is occasionally difficult to make a definite identification of leprosy at this stage because of the vagueness of the clinical picture and the indeterminate nature of the pathological appearance. Skin smear is noncontributory because it is almost always negative for acid fast bacilli. Immunological tests such as lepromin test and lymphocyte transformation response to *M. leprae* are also not helpful in early identification of the disease. Although histopathology is nonspecific it is perhaps the only available test now to confirm the diagnosis of leprosy at this early stage.

Indeterminate

Tuberculoid ← Borderline Tuberculoid ←→ Borderline Lepromatous → Lepromatous

Purely neural

Fig. 1 Indeterminate leprosy phoromicrograph to show perineural inflammation.

TUBERCULOID LEPROSY

Tuberculoid leprosy is a very well recognised form of the disease. Skin lesions are few. Nerve lesions are even fewer. The skin patch is well circumscribed and is easily demarcated from the normal skin. It may be a macule or a plaque or with a raised border. It is often erythematous, occasionally scaly. There may be tingling and numbness over the lesions. Sensations of heat, cold, touch and pain are usually lost in the patch and the loss is easily tested and confirmed. An adjacent peripheral nerve may be so enlarged as to be felt or seen at the edge of a patch.

The term "tuberculoid" is derived from its histopathological appearance which resembles that of tuberculosis. There are large collections of epithelioid cells, occasional Langhans giant cells and many lymphocytes (fig. 2). Tubercles are not so well formed as in tuberculous lesions. However there is a definite clumping of the granulomatous inflammation. Nerve bundles are involved by the granuloma and are extensively infiltrated. In some lesions nerves are totally destroyed and are not identifiable anymore. Skin appendages like sweat and sebaceous glands, hair follicles are also infiltrated and destroyed. The epidermis is flattened and the inflammatory granuloma almost touches the basal layer in many areas.

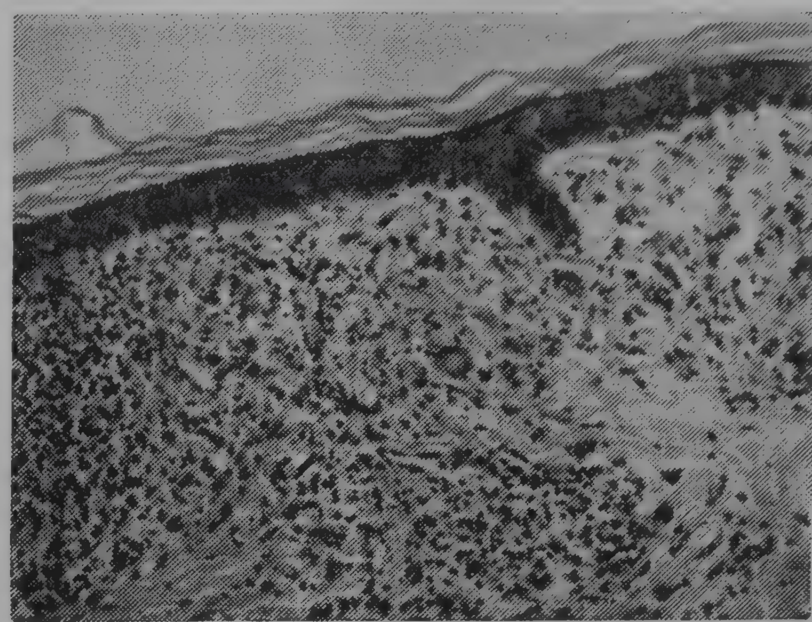


Fig. 2 Tuberculoid leprosy. Note the flattened epidermis and the tuberculoid granuloma coming up to the epidermis.

Acid fast stain of the lesion is not so helpful and organisms are very rare. They are seen inside nerve bundles only if ever present.

As the lesions resolve the nerves show hyalinisation. Sweat and sebaceous glands disappear. Hair follicles atrophy and are lost. But proliferation of fibrous tissue and scar formation is invariably absent. In fact, there is atrophy and wrinkling of the skin.

Occasionally tubercles are demonstrated in regional lymph nodes in tuberculoid leprosy which goes to prove that even in tuberculoid leprosy there is dissemination of bacilli through lymphatics. The disease is contained and localised to a few patches in the skin and a few nerves because of the high immunity present in these patients.

Lepromin test is highly positive and lymphocyte transformation response to *M. leprae* is also very high and they demonstrate that tuberculoid patients possess good immunity to leprosy.

LEPROMATOUS LEPROSY

In lepromatous leprosy the lesions are disseminated. The cutaneous nerves and the skin throughout the body are affected. In the early stage there may only be generalised

erythema of the skin but later well marked gross thickening of the skin and nodule formation are noticed. Glove and stocking anaesthesia is a late manifestation but loss of appreciating heat and cold, and loss of fine touch may be present especially at the ulnar border of the extremities in patchy areas very early in this form of the disease. Motor paralysis is a late manifestation. Oedema of feet and hands may also be seen in an occasional patient. Gynaecomastia and testicular atrophy are not uncommon. Loss of hair at the lateral border of the eyebrows is an early sign but later in the disease hair throughout the body may be lost. Depression and flattening of the nose is a late manifestation. However, blocking of the nose may be the first symptom in some patients. Iritis and iridocyclitis are common complications and are present in majority of the patients.

Pathological changes in the skin are well recorded and easily identified. The epidermis is completely flattened out with loss of papillae. There is a clear area immediately beneath it which separates the granuloma composed of largely macrophages, some plasma cells and a few lymphocytes (fig. 3). Nerve bundles are surrounded by macrophages, so also other skin appendages like hair follicles, sweat and sebaceous glands. Some nerve bundles show an onion peel appearance due to proliferation of the perineurium. Later in the disease all these granulomas fuse together to form a band like infiltrate.

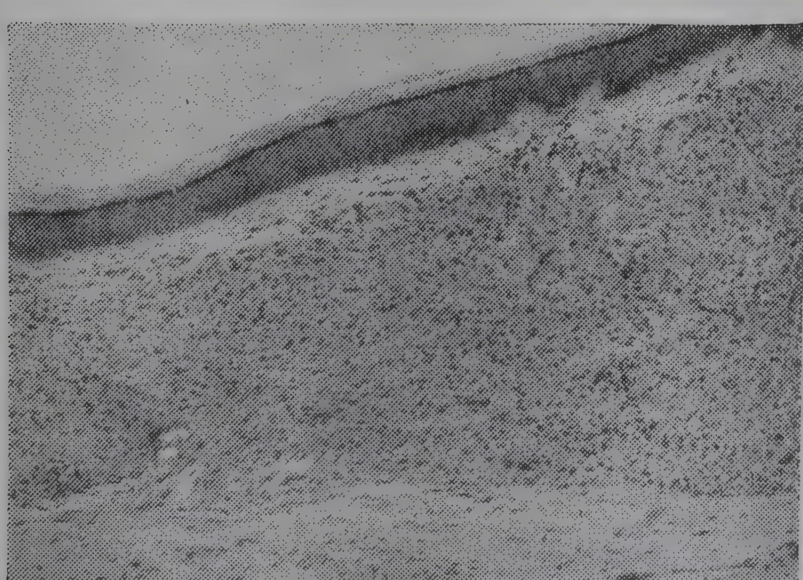


Fig. 3 Lepromatous leprosy. Atrophic epidermis separated by a clear area from the granuloma composed of mabrophages.

Acid fast stain shows many bacilli inside the macrophages, Schawnn cells, perineural cells and arrectores pilorum muscle bundles. Often bacilli are present in endothelium of capillaries and in hair follicles, sweat and sebaceous glands. Nodules in the skin are formed by proliferation of the bacilli filled macrophages. Continuous bacteremia is also demonstrated in well established patients of lepromatous leprosy.

If the lesions heal under treatment, the nerves are hyalinised. The other skin appendages atrophy and disappear. The skin atrophies due to extensive destruction of collagen tissue. Fibrosis of the skin is never seen except in the extremities which have had chronic oedema.

Lepromatous patients have very little, if any, immunity to *M. leprae*. Lepromin test and lymphocyte transformation response to *M. leprae* are negative. The disease spreads through-out the skin and peripheral nerves and also affects the organs of the reticuloendothelial system such as liver, spleen, bone marrow and lymph nodes. Granulomatous lesions of various sizes composed of bacilli filled macrophages are present in these organs. Adrenal glands may also show microgranuloma.

The only organ that is destroyed completely and rendered functionless is the testis. The granuloma infiltrates the interstitial tissue and the seminiferous tubules and destroys them. Gynaecomastia seen in some lepromatous patients may be a sequellae to orchitis and atrophy of testis.

The nasal mucous membrane is involved very early in lepromatous leprosy and some believe that it is the initial site of disease in lepromatous patients. The nasal lesions advance to infiltrate and destroy the cartilaginous and bony framework of the nose producing flat nose deformity.

Leprous episcleritis, scleritis, keratitis, iritis and iridocyclitis are all very well known. Bacilli filled macrophages infiltrate the eye in different sites forming nodules. Initially they are erythematous but as the disease advances impairment of the function of the organ inevitably follows.

Lepromatous leprosy is a slowly progressive disease and in some patients an acute phase is noticed from time to time and is described as "reaction". During the reactive phase erythematous nodules appear on the skin

as "reaction". During the reactive phase erythematous nodules appear on the skin associated almost always with fever often with joint pains and neuritis and rarely with iritis and orchitis. These nodules are called erythema nodosum leprosum and are produced by an acute inflammatory reaction consisting of neutrophil polymorphs infiltrating lepromatous granuloma. During this acute phase acute paralysis of the nerves, acute iritis leading on to blindness, acute arthritis, skin nodules with abscess formation may be present.

BORDERLINE TUBERCULOID LEPROSY

Patients with borderline tuberculoid leprosy from a significant proportion of patients in India. The lesions are usually multiple. They are either nacular or raised with edges fairly well demarcated. Most of the lesions show sensory loss. Only an occasional patient shows positive skin smears.

These patients have a fairly well developed immunity with positive lepromin test and good response to *M. leprae* in lymphocyte transformation tests.

Histopathological appearance resembled tuberculoid leprosy in many respects. The epidermis is atrophic. A clear area separates the granulomatous inflammation from the epidermis. There are collections of epithelioid cells and lymphocytes (fig. 4).

Fig. 4 Bordeline Leprosy. Atrophic epidermis. A tuberculoid granuloma in the corium separated by a clear area fram the epidermis.

Occasional Langhan's giant cells are also present. However, the clumping of epithelioid cells are less evident. Lymphocytes are fewer. Inflammatory granulomas are present in and around all skin appendages. The nerves show intraneural inflammation and destruction. Acid fast stain shows only occasional bacilli inside nerve bundles.

Granulomas in liver and lymph nodes have been observed in some patients with borderline tuberculoid leprosy.

BORDERLINE LEPROMATOUS LEPROSY

These patients resemble lepromatous leprosy in many ways. The skin and nerve lesions are disseminated through out the body. The skin patches may be macules or plaques with indefinite edges. The lesions merge imperceptibly into normal skin. They are symmetrically placed. Often there is a shiny erythema over the lesions. Skin smears are almost always positive for acid fast bacilli.

Immunologically there is very little resis tance in these patients and lepromin reaction is invariably negative. Lymphocyte Transformation response to *M. leprae* although not negative, is poor.

Histopathologically there is atrophy of epidermis with a clear area beneath it separating the granulomatous inflammation consisting mostly of macrophages. A few small collections of epithelioid cells are also seen. Lymphocytes are present in small numbers in and around the granulomas which surround the skin appendages. Nerves show mostly perineural inflammation. However, an occasional nerve shows intraneural infiltration and destruction.

Acid fast stain shows a large number of bacilli inside macrophages, nerve bundles, and arrectores pilorum muscles.

Microgranulomas are demonstrated in liver and lymph nodes. Although they resemble tubercles they are composed largely of macrophages with clumps of acid fast bacilli in them.

COMPLICATIONS OF LEPROSY

(1) *Plantar ulcers:* Due to loss of sensation like touch and pain in the extremities, the protective function of pain is lost. Limbs exposed to constant trauma are not warned of excessive trauma beyond the point of

safety. There is also diminished blood circulation following narrowing of blood vessels. All these factors are responsible for chronic ulcers in plantar surface of foot and in hands. They are not directly due to leprosy and therefore do not contain *M. leprae*. Ulcers at these sites are prevented from healing because of lack of rest to the affected part and continuous trauma permitted by the patient to the ulcerated part due to loss of painful stimuli. Given adequate rest, protection from trauma and secondary infection the ulcers heal fast and well.

(2) *Amyloidosis:* In our experience lepromatous leprosy is the most common disease in India to cause amyloidosis. Amyloid deposits are found in liver, kidney, spleen and adrenal and it belongs to the secondary variety. Amyloidosis must be suspected if there is persistant albuminuria and should be confirmed by biopsy of liver or kidney.

(3) *Tuberculosis:* The common cause of death in an autopsy study by us is tuberculosis. Patients with lepromatous leprosy seem to be prone to develop tuberculous lung, lymph nodes and other organs. Since they come from poor strata of society they cannot afford adequate diet and necessary rest. However, their response to antituberculous therapy is good.

THE MOUSE FOOT-PAD MODEL IN LEPROSY RESEARCH

K. V. DESIKAN

Evolution of experimental studies

There have been several lacunae in the scientific knowledge on leprosy, and one of the major causes for these deficiencies is the fact that the causative germ has resisted every attempt to be cultured in the laboratory. Since their discovery by Hansen in 1874, numerous attempts have been made to culture the leprosy bacilli in artificial medium but without any success. Similarly, several attempts to infect different types of animals have ended up in failure (For review, Prabhakaran 1975). Animals like the guinea pigs, gloden hamsters, monkeys, chimpanzees, even fish and other smaller animals were tried, but the germs failed to grow in them or produce the disease.

A major break through was achieved in 1960 by Shepard, at the Centre for Disease control, Atlanta, U.S.A. (Shepard 1960). Based on the observation that *M. ulcerans* which belong to the same taxonomical family of *M. leprae,* multiplied in the foot-pads of mice, Shepard chose these sites in the mice to inoculate leprosy germs obtained from nasal washings of a lepromatous leprosy patient. The trial yielded fruitful results and bacteria began to grow in the mouse foot-pads. The work was repeated and the growth of bacilli was found to be consistent. The experiments were subsequently reproduced by Rees at the National Institute for Medical Research, London (Rees 1964). Several other laboratories the world over began to use this model for experimental work. In India, this work was successfully reproduced by Karat (1970) Job (1973) and Desikan (1975).

Salient features of experimental leprosy in mice

Before going into the details of experimental leprosy, certain fundamental aspects must be made clear regarding Shepard's mouse foot-pad model which has certainly stood the test of time.

(1) The multiplication of bacilli is strictly local. In other words, the multiplication of bacilli takes place only at the site of inoculation and there is no dissemination to other parts of the mouse by blood or lymph stream. Even local spread to tissues higher up in the limbs does not take place.

(2) The multiplication is limited. The maximum growth reported is a thousand-fold increase. However, on the average, the yield is 100 to 200 times the number of bacilli originally inoculated. This may sound as a high number when we do not have a better animal, but compared to the growth of *M. tuberculosis* in the guinea pig, the multiplication is extremely small. Compared also to the more recent experiments on the growth of *M. leprae* in the Armadillo, the multiplication of the bacilli in the mouse foot-pad is relatively insignificant.

(3) Although there is multiplication of bacilli in the foot-pads, no clinical lesions similar to human leprosy are produced in the mice. There are no skin nodules, no nerve paralysis, anaesthesia or trophic changes. As such the experimental infection as produced in mice is not a true replication of the human disease.

(4) The multiplication of bacilli is not progressive but self limited. After reaching a peak value at the end of 6 months, the number of bacilli remains constant for a time and subsequently there is a fall in the number. Ultimately, the organisms apparently disappear completely.

(5) A long term follow up of infected mice is restricted by the short life-span of mice which is only about 2 years. In a disease like leprosy with a long incubation period and slow development of lesions, it would be necessary to have animals with a long span of life.

(6) Finally, it is evident from the facts mentioned above that experimental leprosy in mice is not identical with the human disease. As such what is seen in the mouse foot-pad does not necessarily represent the human disease. The scientist therefore will have to exercise great caution while interpreting the results in mice experiments. However in the

absence of a more suitable animal, the mouse footpad model helps to provide guide lines to several studies in leprosy.

Method of inoculation, harvest and monitoring of results

An outline of the techniques followed and methods adopted may be briefly described. It is important that the assessment of bacterial growth must be strictly quantitative. An exact and known number of bacilli should be inoculated into mice and after a definite period of time, the total number of bacilli in the foot-pad should be estimated. The bacilli for inoculation are generally collected from skin lesions of leporsy. A biopsy specimen of the skin lesion is collected aseptically. It is minced with a pair of scissors, homogenized in a glass homogenizer and suspended in saline. The number of bacilli per unit volume of the suspension is determined by techniques based on the methods originally described by Shepard and Mc Rae (1968). A modified technique is described by Desikan and Venkataramanaiah (1976). The suspension is diluted and 10,000 bacilli are inoculated into the mouse foot-pad. The mice are kept in proper cages and housed in an air-conditioned room with a temperature ranging between 20°C to 25°C. They are fed on a normal commercial diet. After a period of 6 months, the mice are killed one or two at a time at monthly intervals. The tissue of the foot-pads are pooled, homogenized and bacilli enumerated by standard techniques (Desikan and Venkataramanaiah, 1976).

Growth Curves

There is a distinct pattern of growth of *M. leprae* in the mouse foot pads consistently found in all laboratories (Fig. 1). The growth curve of the bacilli can be divided into 3 phases. In the initial "lag phase" there is no detectable increase in the number of bacilli. In fact, it has been found that there is a sharp fall in the number of bacilli soon after inoculation (Desikan 1975). After the "lag phase" comes the "logarithmic phase" when the bacilli multiply by binary fission. There is thus a sharp increase in the number of bacilli. The third phase is the "plateau phase" which is reached by 210 days. In this phase the number of bacilli remain more or less constant. This, according to Shepard is due to simultaneous multiplication and death of bacilli. This lasts for 6 to 8 months, after which there is a slow fall in the number of bacilli.

Fig 1. Growth curvc of M. Leprae in mouse foot-pad (Desikan, K. V., Leprosy in India 47: 94: 1975)

Use of immunologically suppressed mice

Having noted that there is a restricted multiplication of bacilli in normal mice due to their natural immunity, attempts were made to block the natural resistance of the animal so that the organisms could multiply in its tissues. Cochrane et al (1939) tried to infect monkeys after splenectomy and the same authors tried to bring about immunosuppression of monkeys by blocking their reticulo-endothelial system with Indian ink. (Cochrane et al 1945). They failed in both the attempts to infect the animals. Rees (1966) succeeded in producing a disseminated infection in mice by subjecting the animals to thymectomy and total body irradiation. By this method, bacilli were found in organs in sufficiently large numbers (Desikan and Rees 1973). The yield of bacilli was higher in the footpads when compared to inoculation of normal animals. This was not due to a more rapid multiplication. In other words, there was no shortening of the generation time, but the organisms multiplied for a longer time without being killed in the mouse tissues. The thymectomized irradiated mice are more susceptible and can be infected by a smaller dose of leprosy bacilli, but these animals cannot be considered as suitable models for study of the disease because their normal physiology is so severely interfered with artificially.

Shepard's mouse foot-pad model has therefore been established as an accepted and standard experimental model for more than 15 years (Shepard 1971). The results are found to be consistant and reproduced uniformly

by all the laboratories. The animal used is readily available and easy to handle and maintain. While there is a wide range of publications of the experimental model for several studies, some of the more important ones are listed below:

1. *Preliminary screening of drugs:* This is the most important application of the mouse foot-pad model and an extensive work has been done in this field. In the course of the past 10 to 15 years, more than 200 drugs have been screened and very important data obtained (Shepard et al. 1976). Before the advent of the experimental animal, new drugs against leprosy had to be tried only on patients, which made it extremely difficult. Now a new drug can be tried for its efficacy against leprosy, its toxicity at therapeutic levels, its action as a bacteriostatic or bactericidal agent, its exact mode of action and its pharmokinetics. Infact, it has almost now become obligatory that any new drug is first tried in mice and only after it is found to be safe and effective by this preliminary trial that it is considered for further therapeutic use.

2. *Detection and confirmation of sulphone resistance:* Emergence of sulphone resistance was considered for several years, but there was no means of establishing the same since there was no known method of growing *M. leprae.* With the advent of the mouse foot-pad model, this has now become possible. Pettit and Rees (1964) first made the experimental trials. Several sulphone resistant cases have been detected and confirmed in Malaysia and Ethiopia. Sulphone resistant cases have also been identified and confirmed in India (Roychaudhury and Desikan 1975). The procedure employed in these investigations is that bacilli obtained from suspected cases of sulphone resistance are inoculated to mice. The mice are then fed on diets containing D.D.S. at concentrations to produce desired, therapeutically effective blood levels of D.D.S. in the mice. If the drug inhibits growth of bacilli in the foot-pads, the germs are D.D.S. sensitive. On the other hand, if the germs continue to multiply in spite of the administration of the drug, they should be considered as being resistant. Studies carried out recently at Chingleput have shown that out of 37 cases suspected to be sulphone resistant clinically, 29 cases were confirmed to be drug resistant by animal experiments.

3. *Identification of Mycobacteria claimed to be M. Leprae:* There have been claims of culture of *M. leprae* in vitro. There must be a method to confirm whether they are *M. leprae* or not. So far the only method adopted was the failure of the germs to grow in artificial medium, but this negative finding is subject to several errors. If the germs are inoculated into mice foot-pads, and if they exhibit the normal growth curves, a strong evidence would then be in favour of their being *M. leprae.* The procedure is now accepted as one of the methods to establish the identity of *M. leprae.*

4. *Assessment of viability of M. leprae:* It would be possible by this method to establish whether a given sample of *M. ledrae* are alive or dead. These bacteria may be collected from treated cases to find out the rate of killing of *M. leprae* by treatment. *M. leprae* collected from environs may also be tested for their viability using the mouse model.

5. *Tests for experimental vaccines against leprosy:* These tests could also be carried out before a vaccine is possibly tried in human subjects. This would be very impotant in future since there is a concentrated effort by some laboratories to develop a vaccine. It has been found for example, the experimental vaccines prepared from oil treated cell walls were found to provide as much protection as live BCG in experimental leprosy (Shepard and Ribi 1968).

There are several other uses, both in academical as well as in applied researches, for the mouse foot-pad model. In spite of several short-comings, the experimental transmision of Leprosy to mice has proved to be a dependable technique for Scientific investigation. It has thrown light on many aspects of leprosy about which there was total ignorance hitherto. Meticulously used, the mouse foot-pad model is at present a great asset and is a very useful tool to the investigating scientist.

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THE ARMADILLO IN LEPROSY RESEARCH

WALDEMAR F. KIRCHHEIMER

Inability to culture *Mycobacterium leprae* and failure to have on hand a valid animal model for the study of the disease in man were the main retarding factors in gaining an understanding of the disease and the germ. There were no answers to the following fundamental questions:

1. How, and how frequently is the leprosy bacillus transmitted in endemic areas?

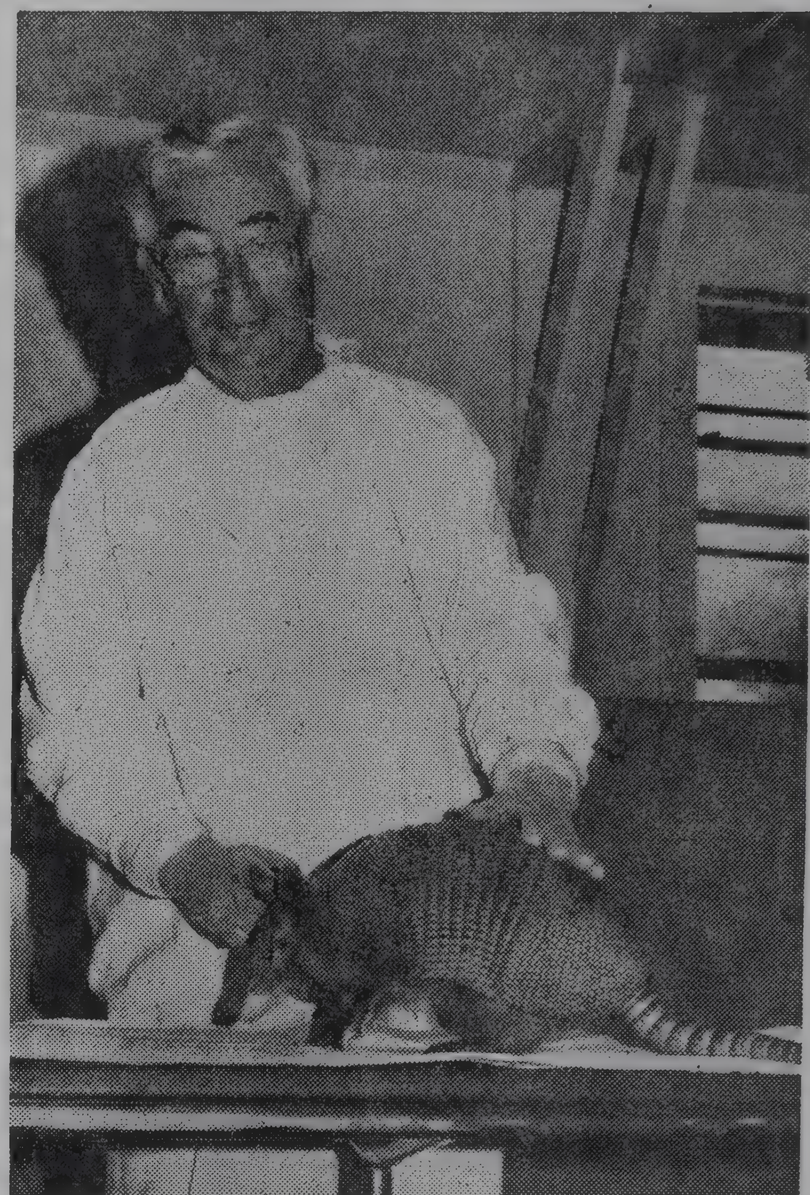
2. Why do most persons living in povetry, in stable communities in highly endemic surroundings escape leprosy?

3. Why are there such dissimilar clinical diseases as tuberculoid and lepromatous leprosy?

4. Does lepromatous leprosy result from higher infectious doses, or more virulent bacilli, or greater host susceptibility?

With the exception of the introduction of the sulfones into leprosy therapy in the 1940s (1) nothing significant had happened until 1960 to move leprosy research out of the doldrums. In that year Shepard (2) reported limited multiplication of *M. leprae,* restricted to the cool tissues of the mouse foot pad. Because this was reproducible and of distinctive pattern the mouse foot pad has been used in viability determinations of *M. leprae,* as one of the means of identifying (2), in drug screening and in determining drug resistance of the bacilli (3, 4). It has not, however, provided the needed bacteria or the needed animal model. Neither was this gap closed by its offspring, the immune-suppressed mouse (5) which, however, engendered exploration of the role of cell mediated immunity (CMI) in leprosy (6).

In 1971 and 1972 Kirchheimer and Storrs (7, 8) transmitted leprosy to armadillos. Kirchheimer, *et al.,* (9) also showed that 1 gram of infected armadillo tissue contained



The author with a healthy nine-banded Armadillo.

from 100 to 1000 times more leprosy bacilli than 1 gm of human skin leproma. Kirchheimer and Sanchez (10) showed additionally that the percentage of armadillos developing disseminated leprosy increases with the size of the infecting dose. If infected intravenously with several hundred million leprosy bacilli all armadillos seem to be "susceptible." Since one can readily transmit leprosy from armadillo to armadillo without any apparent change in the microbe (11) and because one can harvest around 10 billion (10×10^9) *M. leprae* from 1 gram of their spleens, livers, lymph nodes and subcutaneous lepromas

(7-10), an abundant source of leprosy bacilli has finally become available and a major obstacle to progress has been removed.

Epidemiologists and geneticists have long suspected that excessive susceptibility to leprosy might have a genetic basis (12, 13). Clinical and experimental leprologists had known for many years that *M. leprae* multiplied best in the cooler tissues of the human body (14) and in the cooler parts of the body of mice (15). Nine-banded armadillos were known to have a relatively low body temperature (16). They live for 12 to 15 years. They give birth regularly to monozygous, genetically identical quadruplets. In addition they are readily available in Louisiana and other Southern States of the Union. These characteristics made nine-banded armadillos an ideal candidate for leprosy transmission experiments, with hope for rich harvests of bacilli and for developing the needed model for the study of fundamental and applied aspects of the human disease leprosy.

Because armadillos occur only in the warmer parts of the Americas search for indigenous susceptible mammals is carried out in Germany, India and South Korea, involving, respectively, the European hedgehog (17), the Indian pangolin, the slender loris (18, 19) and the Korean chipmunk (20).

A South American armadillo, *Dasypus sabanicola,* is being developed as a source of leprosy bacilli at the Instituto Nacional de Dermatologia, Caracas, Venezuela (21).

Armadillos have not yet been bred under controlled conditions. This is a prerequisite for genetic leprosy susceptibility studies. An additional requirement for Carville's objective to develop the ninebanded armadillo into a model for a comprehensive investigation of leprosy is the availability of a test which predicts the degree of susceptibility of armadillos prior to infection. Experiments to develop such a test are being conducted at Carville. They are based on an armadillo's capability to develop delayed type hypersensitivity (tuberculin-type) to *M. leprae* protein (22). Non-leprous suceptible animals are required for investigating postulated modes of transmission of leprosy (23), exploration of the mechanism of resistance and chemo- and immuno-prophylactic studies.

Development of a susceptibility-test in uninfected armadillos and successful breeding under controlled conditions are very important stepping stones toward Carville's ultimate objectives:

1. The investigation on an animal model of the validity of the genetic hypothesis of susceptibility to leprosy.
2. Investigation of the mechanism of susceptibility and resistance in leprosy.
3. Investigation of the modes of transmission of leprosy.
4. Investigation of the efficacy of various prophylactic measures against leprosy, including immuno and chemoprophylaxis.

The predictive value of the susceptibility test must be validated with a subcutaneous infection dose of *M. leprae* which gives disseminated leprosy to less than 10 percent of the challenged armadillos in 3 to 4 years.

In our experience this dose is less than 10,000 *M. leprae*.

The great importance of the potentially unlimited supply of leprosy bacilli in biomedical leprosy research is now generally recognized. Examples of this are first, the World Health Organization (WHO) sponsored studies of the feasibility to replace hard-to-get human tissue-derived lepromin H with armadillo tissue-derived lepromin A. The results to date show good correlation between the Fernandez and Mitsuda reactions obtained in patients with various types of leprosy and in non-leprous persons in endemic areas with lepromin H and Carville's lepromin A. The Fernandez and Mitsuda reactions to lepromin are routinely used to monitor the state of resistance of leprous individuals and of non-leprous exposed persons. Positive reactors whether or not they have leprosy seem more resistant to *M. leprae* than non-reactors. Lepromin therefore plays an important part in the management of leprosy. There is little doubt that lepromin A soon will replace lepromin H.

Another important project which owes its existence to the availability of abundant amounts of leprosy bacilli from armadillos is WHO's Immunology of Leprosy Project (IMMLEP). The immediate objective of this work is preparation of pure specific antigens from *M. leprae*. Such antigens might be of inestimable value as diagnostic and epidemiological tools, as an immunological reagent for

incorporation into a vaccine, and as a therapeutic weapon that could perhaps be used to prevent some of the most adverse complications of leprosy such as nerve damage and Erythema Nodosum Leprosum which are immune pathological phenomena. It is also hoped that some antigenic fractions of the bacilli might restore a state of natural resistance to patients cured of lepromatous leprosy but still at risk of relapse. Eventually perhaps a vaccine might be produced that can raise the level of resistance against leprosy in an endangered population, ultimately contributing to the control of leprosy.

A purified *M. leprae* protein that elicits delayed type hypersensitivity reactions in the skin of armadillos vaccinated with heat-killed *M. leprae* has recently been prepared in our laboratory (22). As we had pointed out in our publication Dharmendra in 1941 (Lep. India 13:89) had prepared for the first time a protein antigen from defatted *M. leprae*. He concluded that this protein was the active principle of the lepromin responsible for the positive lepromin reaction in tuberculoid cases of leprosy. The antigen produced no reaction in lepromatous cases. However, because of the limited supply of the human lepromatous material and because of the very small amount of the protein antigen that could be prepared from the bacilli, this antigen could not be utilized for routine testing of cases of leprosy of different types and of healthy persons.

Judging from the results of a limited trial with our armadillo tissue-derived *M. leprae*-protein in India on patients with different forms of leprosy and non-leprous disease this skin test antigen does not cross-react with tuberculin and accords with a person's Mitsuda test response (24).

Leprosy bacilli separated from experimentally infected armadillos are used at Carville to study the metabolic characteristics of *M. leprae*. The final objective of these studies is to find a rational basis for culture-attempts and for specific anti-*M. leprae* drugs. Recently Prabhakaran, *et al.* (11) have shown that the *o*-diphenoloxidase remains unaltered in the passage of the bacilli from the human host to the armadillo indicating that the enzyme discovered by Prabhakaran (25) is an intrinsic characteristic of the leprosy bacillus. These results and the ones obtained in the WHO lepromin study also provide additional evidence that the bacteria recovered even after passage from armadillo to armadillo are in fact *M. leprae*.

Finally, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health in Bethesda, Maryland (U.S.A.) has awarded Carville a contract under which a sizeable colony of *M. leprae* infected armadillos is maintained. This serves as a continuing source of materials for scientists whose research projects have been approved by the National Institutes of Health.

Man is the only proven natural host of *Mycobacterium leprae*. Leprosy-like mycobacterioses have been described in Indonesian water buffalos (*Bubalus bubalus*) by Lobel (26, 27) and by Machicao and LaPlaca (28) in Bolivian frogs (*Pleurodema ciner*. and *Pleurodema marmoratus*). The mycobacteria just like *M. leprae* and *Mycobacterium lepraemurium* have not been cultured. Their bacteriologic characteristic such as d-dopa oxidation (29), the pyridine extraction test (30) and pattern of mouse foot pad multiplication (2) are unknown. The relationship of these acid-fast bacteria to *M. leprae* is unknown.

In 1975 Walsh, *et al.* (31) reported a leprosy-like disease among armadillos (*Dasypus novemcinctus*) in Southern Louisiana West of the Atchafalaya River. This mycobacteriosis was said to have a prevalence of 10 percent and the histopathologic characteristics of experimental leprosy in the armadillo as first described by Kirchheimer, *et al.* in 1972 (9). The acid-fast bacilli were reported to be indistinguishable from *M. leprae*. Investigations by others have not so far confirmed the occurrence of leprosy or a leprosy-like mycobacteriosis in wild armadillos.

Kirchheimer (32) has recently summarized the results of his own investigations at Carville. No leprosy-like disease was found in any of the 365 armadillos examined in his laboratory. It is of particular interest that 75 of these armadillos were caught by personnel of the Louisiana State Wildlife and Fisheries Commission in the area where Walsh, *et al.*, say they had found the leprosy-like disease. Duplicate specimens of these particular armadillos were examined by the Epidemiology Investigation Service of the National Center for Disease Control, Atlanta, Georgia, likewise with negative results.

Munoz Rivas (33) recently has autopsied 80 aramadillos caught in the most leprosy-endemic part of Colombia, South America

without finding leprosy-like disease. Innami from the Santa Isabel Leprosarium and Alvarenga (34) from the Health Ministry in Asuncion did not find leprosy in armadillos in Paraguay.

Both Kirchheimer and Munoz Rivas have found culturable acid-fast bacilli associated with armadillos. Rivas can culture them regularly from the mesenteric lymph nodes and Kirchheimer has found them in approximately 5 percent of armadillos from various parts of Louisiana. In one instance the bacteria were identified as *Mycobacterium pereginum* by Freerksen at the Borstel Institute in Germany.

Filice, *et al.* (35) from the Epidemiology Investigation Service of the National Center of Disease Control did not find any correlation between contact with armadillos and leprosy in man in Louisiana.

In summary the armadillo has amply fulfilled the promise of an ample supply of *M. leprae,* essential for various research projects the world over and as a source for lepromin. Concerning the availability of the armadillo for the comprehensive study of fundamental areas of leprosy we hope that controlled breeding and a valid susceptibility test, the necessary prerequisites, will be accomplished by 1982.

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MICROBIOLOGY OF MYCOBACTERIUM LEPRAE

S. R. PATTYN

1. Morphology

M. leprae when stained by the Ziehl Neelsen procedure is an acid-alcohol fast, weakly curved, bacillus, 0.3—0.4 μm×4—7 μm showing sometimes a metachromatic granule either near a pole or in the center. The nature of these granules has been much discussed but has never been accurately defined, they have been said to be more numerous in untreated, active cases.

Leprosy bacilli aggregate frequently in round to oval clumps, called globi, the organisms being situated in paralel bundles. It is unknown if this is the result of some product secreted by the bacilli or if it is the result of phagocytosis and some action of the host cell on the bacilli.

Very frequently bacilli stain irregularly, giving rise to granular forms. Since the beginning of the century, granular bacilli have been suspected of being dead organisms. In recent years this has been proven to be correct (Rees and Valentine, 1962; Shepard and McRae, 1965) and to be valid for tissue sections as well (Levy e.a., 1969). This allows the evaluation of clinical and experimental specimens, not only in terms of the total number of bacilli present as expressed by the "Bacteriological index", but also by the determination of the percentage of solidly staining, living organisms, as expressed by the "Morphological index" or "solid ratio".

Acid fastness in Mycobacteria has been shown to be related to their lipids, in particular the mycolic acids. The presence of mycolic acids in *M.* leprae was first demonstrated by Etemadi and Convit (1974). The large amounts of *M. leprae* obtainable from armadillo tissue allowed a thorough chemical study of the cell walls (Draper 1976). Like other actinomycetales *M. leprae* has in its walls mycolic acids, aribinogalactan and peptidoglycan. The two mycolic acids are different from those of *M. tuberculosis, M. microti, M. lepraemurium, M. vaccae* and *M. scrofulaceum.* The peptidoglycan contains diaminopimelic acid, alanine, glucosamine, murein and substantial amounts of glycine. The simultaneous occurrence of glycine and diaminopimelic acid in bacteria is rare and it is absent from the mycobacteria analysed thus far. At the present time this is an important differential character of *M. leprae.* Fisher and Barksdale (1971, 1973) claimed that the acid fastness of *M. leprae* was extractable with pyridine, and that this was absolutely specific for *M. leprae,* so much so, that this character could be used as an identification test for the species. However Skinsnes et al. (1975) have shown that pyridine extractability of acid fastness is a characteristic of aging, non viable bacilli, and not at all a specific character of *M. leprae.*

In the electron microscope shadowed preparations of suspensions of *M. leprae* reveal also uniformly dense and beaded granular forms of the bacilli. Very frequently a peripheral halo is observed around the bacilli. Detailed studies with the negative staining technique of this halo have not been reported. Such a study was performed by Draper and Rees on tissue derived *M. lepraemurium* and the halo was found to correspond to bundles of fibrils twisted around the organisms.

After shadowing or negative staining of *M. leprae* suspensions, intertwingled paired fibrous structures 100-300 A in width and forming a network in the walls, can be observed. Some of these threads surround the bacillary body parallel with the short axis and have been called "band like structures" by Nishiura et al. (1969).

In ultrathin sections *M. leprae* has a cell wall 15-20 nm thick, surrounding a cytoplasmic membrane. This is a unit membrane consisting of two dense layers about 3 nm in width, enclosing a 3-4 nm interspace

layer of low electron density. The cytoplasmic membrane gives rise to mesosomes extending into the cytoplasm. Cell division is by transverse fission.

2. Culture

Although numerous authors have claimed to have cultivated *M. leprae* in vitro, none of them have proved that there was definite multiplication nor that the cultures obtained were *M. leprae*. Criteria that can be used to apply to claims of pretended in vitro cultures of *M. leprae* are:

1. The procedure should be successful in a high percentage of attempts, when bacillary rich material, derived from untreated humans or experimental animals is used. Multiplication should be regular and of the order of 100 at least. It should be proven that the bacilli at the end of an experiment are viable.

2. All strains obtained should be identical in many if not most in vitro characters (some biochemical tests could be different as well as some antigenic characters) including drug sensitivity patterns.

3. All strains obtained should be different from presently known mycobacterial species.

4. The strains obtained should behave in experimental animals in an identical way as *M. leprae*, directly derived from human tissue.

5. Lepromin preparations prepared from the cultures should give negative Mitsuda reactions in lepromatous forms of the disease and positive reactions in tuberculoid cases. Up to the present no cultures have been produced that satisfy the above criteria, although cultivation attempts, mostly empirical, have probably been undertaken by the millions (Pattyn, 1973).

In order to come to a more rational approach of the problem every kind of information concerning metabolic activities of *M. leprae* are extremely important.

This information can derive from enzymic or metabolic studies performed with suspensions of *M. leprae* p.ex. the incorporation of radioactive substances in such suspensions (Tepper, 1971) or from direct observation through ultramicroscopic histochemistry.

One of the main difficulties for the first approach is the purification of suspensions of *M. leprae* from host tissue, while viability of the bacteria is maintained. Ultramicroscopic histochemistry is limited in its possibilities. Studies on suspensions of *M. leprae* (Prabhakaran, 1967) showed that the organism possesses cytochrome C oxidase, meaning that it is an aerobic organism. The presence of cytochrome C oxidase has been confirmed by EM histochemistry and is further in line with the fact that metronidazole, a drug almost exclusively active against anaerobic organisms is ineffective against *M. leprae* in the mouse (Pattyn c.a. unpublished results).

Prabhakaran detected in the same suspensions the following enzymes: succinate and lactate oxidases, a very low catalase a high peroxidase activity and 3, 4 hydroxyphenyl alanine oxidase.

Preliminary results of EM histochemistry (Jacob and Pattyn unpublished results) failed to reveal catalase in *M. leprae*, while peroxidase activity and succinate dehydrogenase were detected in the mesosomes. The latter enzyme was also present in the phagolysosome wall surrounding the leprosy bacilli.

Intensive search of inventive biochemists and microbiologists should reveal more of the biochemical activities of *M. leprae* which should give some clues on the growth requirements of the organism.

Prabhakaran and Kirschheimer (1966) have described dihydroxphenylalanine (DOPA)-oxidase in suspensions of *M. leprae*. They claim that this enzyme is absolutely characteristic of *M. leprae*, since it fails in all other species of Mycobacteria. We were unable to confirm this, moreover DOPA is a compound that is oxidized by air within 3 to 4 hours (Unpublished results).

The drug dapsone is bacteriostatic for *M. leprae* in very low concentrations: MIC=0.02 μg/ml. It is thought to inhibit the incorporation of para-aminobenzoic acid (PABA) into dihydrofolate. Its action is antagonized by PABA but in very high concentrations only. This could be the result of lack of penetration of PABA into the *M. leprae* cells (Shepard, 1967).

M. leprae is not cultivated in vitro, can now readily be transmitted to animals

(Shepard, 1960): normal mice (footpad, tail and ears) rats, hamsters and armadillos, and immunosuppressed mice and rats. The evolution of the infection, particularly in the mouse footpad, is characteristic for *M. leprae* when compared with other mycobacteria (Pattyn, 1965). The generation time during the logarithmic phase of multiplication in the mouse footpad is 11-13 days, and has been identical for all strains measured, dapsone sensitive or resistant. Isolates of *M. leprae* in mouse footpads were found to differ in two related properties: the average rate of growth between inoculation and harvest and the number of bacilli in the harvest. The growth between inoculation and harvest covers the logarithmic phase of the growth curve and the lag phase. Since the logarithmic phase is constant, the duration of the lag phase is responsible for the observed difference. "Fast" strains reached more than $10^{6.1}$ per harvest, whereas for "slow" strains the harvests were below $10^{5.6}$, all strains studied formed a continuous spectrum between these two extremes. Slow strains differ from fast strains by having fewer generations of growth. There is no evidence that this characteristic plays a role in human disease.

3. Antigenic structure

Until recently the antigenic analysis of *M. leprae,* mainly in immunodiffusion tests, has been hampered by the difficulty to obtain sufficient amounts of purified bacilli from human lesions and the preparation of potent hyperimmune sera. Abe *et al.* (1970, 1972) found 2 antigens in human leprous nodules: a protein antigen specific for *M. leprae* and a polysaccharide antigen common to other mycobacteria.

Navalkar (1971) found 2 antigens common to other mycobacteria and 3 antigens specific for *M. leprae*.

More recently, Stanford (1976) working with *M. leprae* ultrasonicates prepared from infected armadillo tissue was able to detect 12 antigens. Six of these are antigens common to all mycobacteria, 4 are species specific and 2 of uncertain position. The remarkable thing is that *M. leprae* does not possess any of the antigens common to either the slow or fast growing *Mycobacteria,* a deficiency that is only found in *M. vaccae*.

Conclusion

In the absence of in vitro cultures of *M. leprae,* the knowledge on the microbiology of *M. leprae* is very limited. However intensive research during the last 2 decades has allowed the introduction into clinical leprosy of the morphologic index as a very important aid. The availability of large amounts of *M. leprae* from armadillo tissue has lead to a detailed characterization of the chemistry of the cell walls of *M. leprae* and its intracellular soluble antigens. The importance of this knowledge has recently been illustrated by their application to a claim of a successful in vitro culture of *M. leprae* (Stanford *et all*. Int. J. Leprosy, in press). Continued efforts by inventive biochemists and microbilogists should lead to increasing knowledge concerning this parasite, to allow a better fight against it.

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ACID-FAST AND NON ACID-FAST FORMS OF *M. LEPRAE*— METHODS OF STAINING, AND THEIR SIGNIFICANCE

J. DELVILLE

In classical text books Hansen's bacillus is described as an acid-alcohol-fast non cultivable organism, belonging to the genus Mycobacterium.

The Ziehl-Neelsen staining technique has been, for long, the only method in use for the routine microbiological diagnosis of mycobacterial infections and particularly, leprosy.

Acid-fastness is considered as a specific property of Mycobacteria, related to the presence of mycolic acid and high lipid content in the cell wall. Nevertheless all Mycobacteria are not always necessarily acid fast. Moreover Asselineau (1966) gives the following definition of acid-fastness: 'Acid-fastness is the property possessed by the majority of Mycobacteria, at a certain moment of their evolutionary cycle, of being stained with phenolic fuchsin and resisting decoloring with acids and alcohol'.

This definition implies the possibility of a non acid-fast stage, related to an eventual cycle of certain Mycobacteria.

This, indeed, seems to happen with Mycobacterium leprae.

By using the Ziehl-Neelsen staining as the only method for the microbiological diagnosis of leprosy, it comes out that the etiological agent of the disease can not always be detected in all leprosy patients.

Consequently it has become a matter of common knowledge and a classical concept that *M. leprae* may be very scanty or even not detectable in some lesions. This happens more particularly in tuberculoid cases. Nevertheless typical inflammatory lesions are present with involvement of peripheral nerves and it is difficult to assume that such lesions may be produced in the absence of the etiological agent of the disease.

There is no doubt at present that the Ziehl-Neelsen method fails to detect *M. leprae* in some lesions where other techniques are able to identity them regularly.

So it becomes questionable if *M. leprae* is always acid-alcohol-fast. As early as 1909 Arning and Lewandowsky did already emphasize the fact that *M. leprae* is not always stainable with Ziehl-Neelsen method, particularly in tuberculoid lesions, but is detectable with Gram stain.

The presence of non acid-fast forms in leprosy has been confirmed by Rodriguez, Mabalay and Tolentino (1933), Rao (1935), Manalang (1938), Chatterjee (1965) and ourself (1974-1975).

Since Arning and Lewandowsky, other and more reliable staining methods have been devised and introduced for the microbiological diagnosis of leprosy.

The morphological identification with specific staining methods remains as yet the only means in routine diagnosis of leprosy. The mouse foot-pad inoculation is indeed not applicable for diagnosis in general practice.

Consequently we will consider and discuss the most reliable and wide-spread methods useful in the microbiological diagnosis of leprosy.

STAINING TECHNIQUES

Appropriate fixation is essential prior to staining.

Smears are heat fixed preferably after fixation in formalin vepour for 5 minutes.

Biopsies should be fixed as soon as removed. The thickness of the the tissue blocks should not exceed 5 millimeter for ready penetration of fixing fluid.

The most widely used fixing agent is 10% formalin (1 volume of 40% formaldehyde in 9 volumes of water).

Some prefer Bouin's or Zenker's fixatives. After Zenker's, sections are no more suitable for immuno-fluorescent techniques.

ZIEHL-NEELSEN

carbol fuchsin:	Basic fuchsin	1 gr.
	Phenol	5 gr.
	Alcohol 94%	10 ml.
	Distilled water q.s. to	100 ml.

Smears and tissue sections (after deparaffinization and dehydration) are stained in Carbol-fuchsin without heating, for 20 to 30 minutes.

After washing in tap water, decolorize with 0.5% hydrochloric acid in 70% alcohol.

Wash in water and counterstain with 1% methylene blue or malachite green for smears and Carazzi's hematoxylin (according to Langeron) for tissue sections.

Carazi's hematoxylin:

Distilled water	400 ml.
Glycerol	100 ml.
Potassium alum	5 gr.
Potassium iodate	0.1 gr.
Hematoxylin	0.5 gr.

This solution must be ripened for a few days.

Sections are stained during plus-minus 10 minutes in hematoxylin, washed in slightly alkaline water to become blue, washed in tap water, dehydrated and mounted in Canada balsam or permount according to the classical technique.

WADE-FITE

Fite (1938) emphasized the difficulty of demonstrating the organisms of leprosy in paraffinized tissues and Faraco (1938) showed that, by ordinary methods of demonstrating acid-fast organisms, the lepra bacilli are often not acid-fast.

They devised a method of oiling the sections before staining with carbolfuchsin. The oiling restores the acid-fastness by inducing an artificial acid-fastness. According to Hauduroy (quoted by Asselineau): 'artificial aicd-fastness is only observed in the case of bacilli belonging to the genera Mycobacterium, and Corynebacterium'.

We are regularly using the Wade-Fite method, derived from the Fite-Faraco technique, according to the description given in 'histopathologic technic and practical histochemistry' by R. D. Lillie (1965) with some slight modifications as follows:

Fix preferably in Zenker's fluid or in formalin. Embed in paraffin as usual. Sections are mounted on slides with Mayer's glycerol albumin. Dry overnight at 37°C.

1. Deparaffinize in 2 parts rectified turpentine, 1 part paraffin oil, 2 changes in 5 minutes.
2. Drain, wipe back and edges of slide, blot with filter paper until section appears opaque. Let stand in water until staining.
3. Stain 1 to 2 hours in carbolfuchsin. Wash in water.
4. Cover slide with 37-40% formaldehyde (reagent grade) for 5 minutes.
5. Extract 5 minutes in 5% (v/v) sulfuric acid. Wash in water.
6. 1% potassium permanganate, 3 minutes.
7. Bleach with 2% oxalic acid, preferably less than 30 seconds, and not more than 60 seconds. Use 5% oxalic acid if sections do not decolorize readily.
8. Stain 10 minutes in Carazzi's hematoxylin as after Ziehl-Neelsen.
9. Dehydrate and mount preferably in synthetic resin (permount or the like) according to the classical technique.

In most biopsies of leprosy lesions showing no or only few bacilli with the classical Ziehl-Neelsen method, several to very numerous bacilli and even globi become visible with the Wade-Fite technique. This technique is however not suitable for smears.

NYKA METHOD

Nyka (1967) described a method for staining both acid-fast and chromophobic tubercle bacilli with carbolfuchsin. Prior to carbolfuchsin staining (i.e. Ziehl-Neelsen), slides are oxidized in a 10% periodic acid aqueous solution during 4 hours for tissue sections and 4 to 24 hours for smears.

LEGEND TO FIGURES

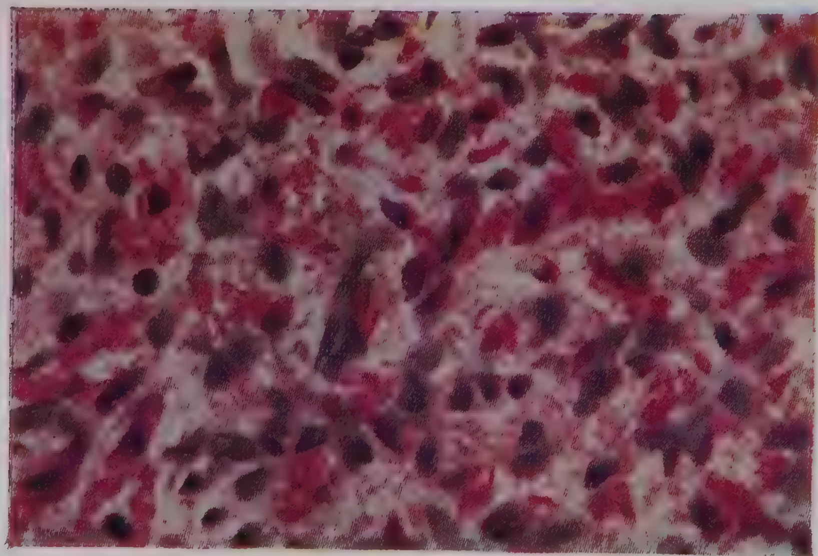
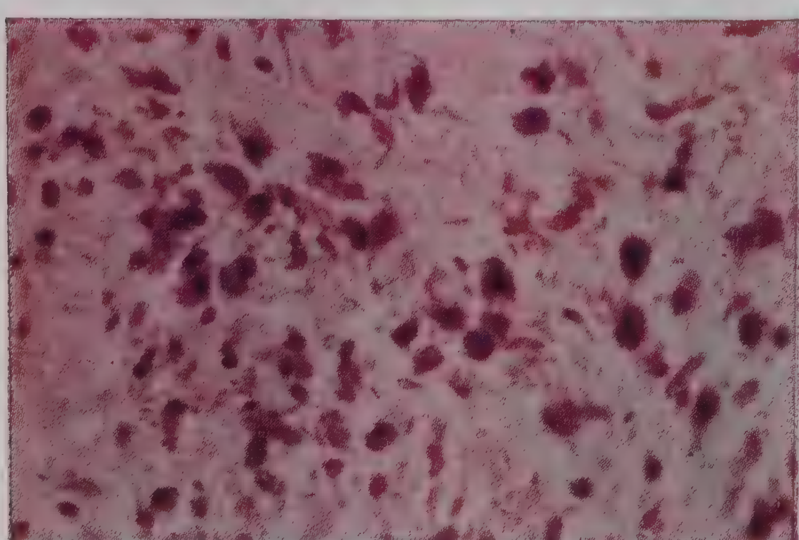
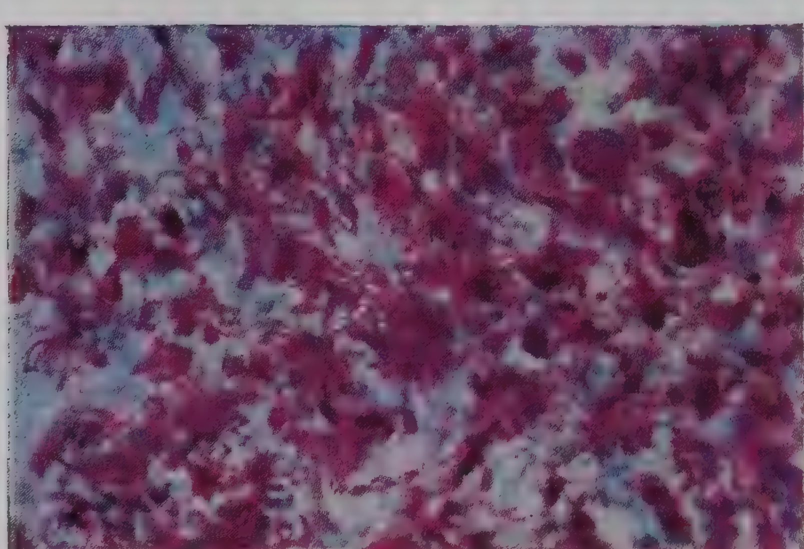


Fig 1. Section of human leproma (non-treated early lepromatous patient).

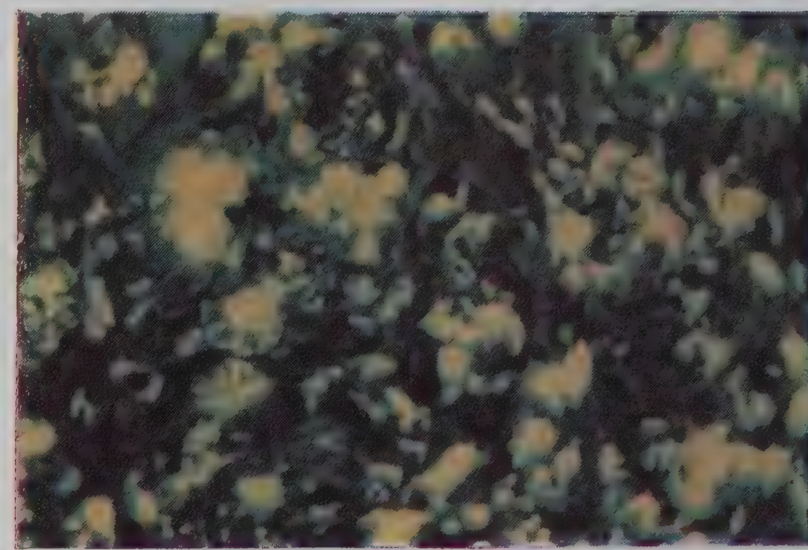
(a) Ziehl-Neelsen stain — × 215



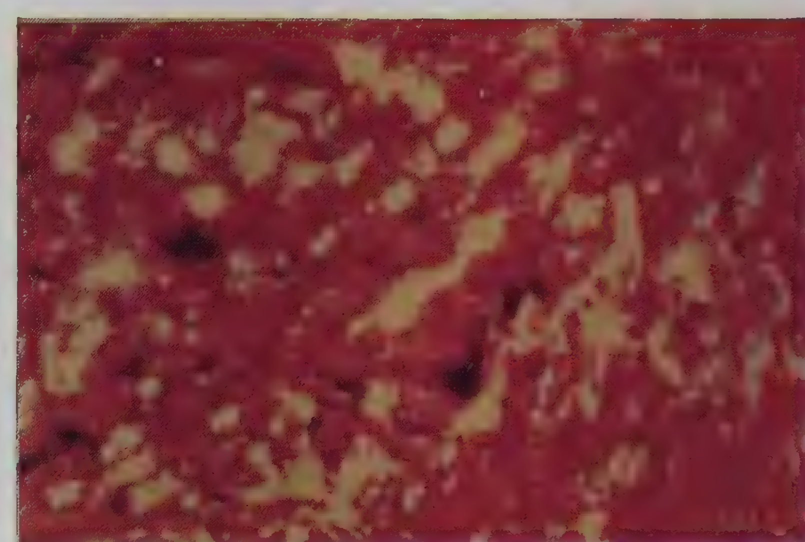
(b) Wade-Fite stain × 215



(c) Nyka stain — × 215



(d) Auramine stain — × 215



(e) Immunofluorescence with anti-diphtheroid serum and counterstain with Evans blue — × 215

No striking difference between the different staining techniques, but bacilli and globi are more deeply stained with Wade-Fite and Nyka stain and seen some more numerous.

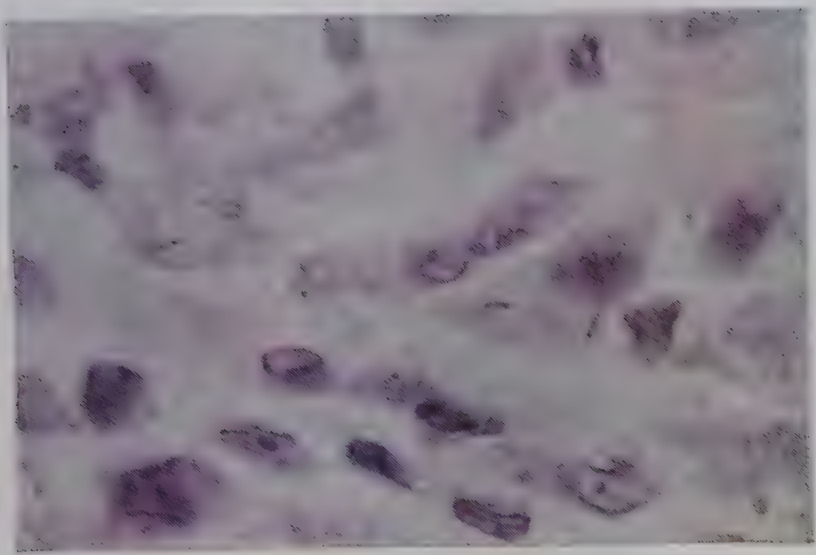
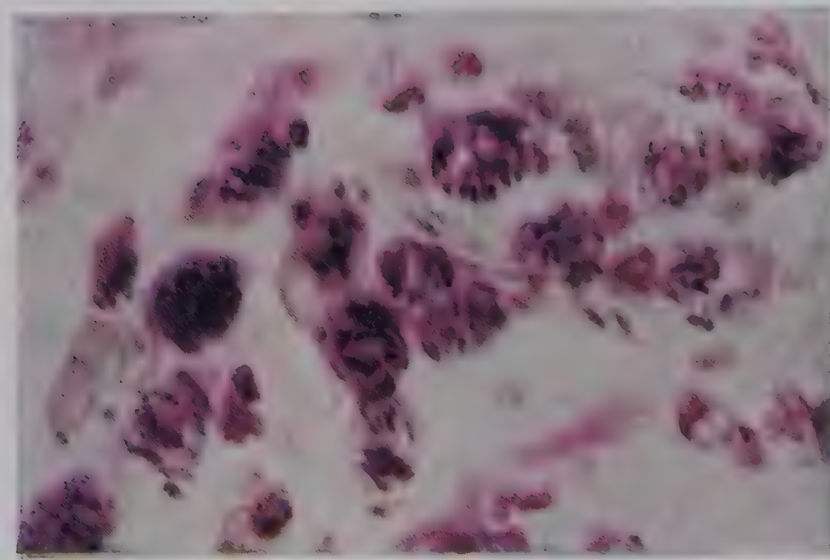


Fig 2. Section of human leproma (treated patient).
(a) Ziehl-Neelsen stain : few bacilli are visible — × 535



(b) Wade-Fite stain : numerous bacilli and globi — × 535

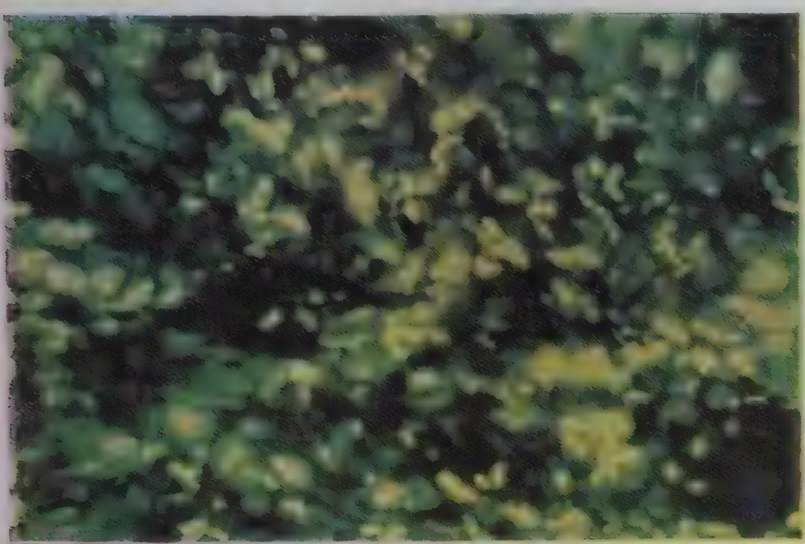
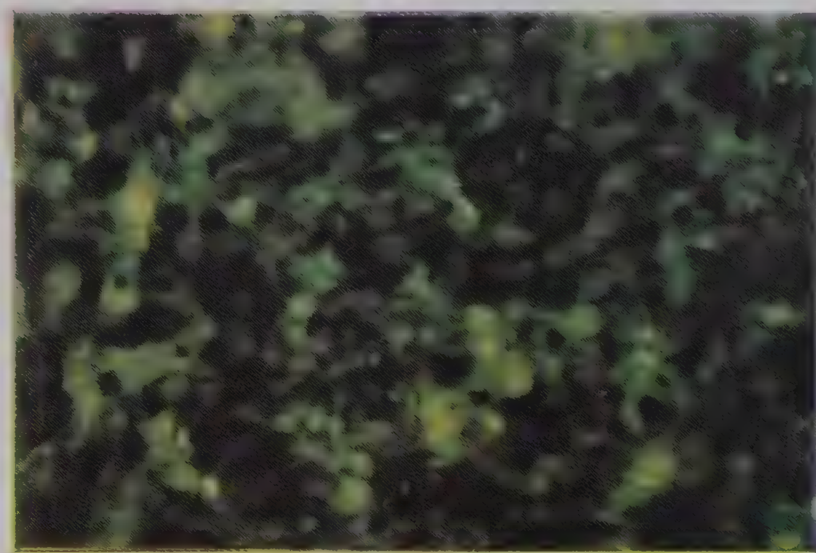
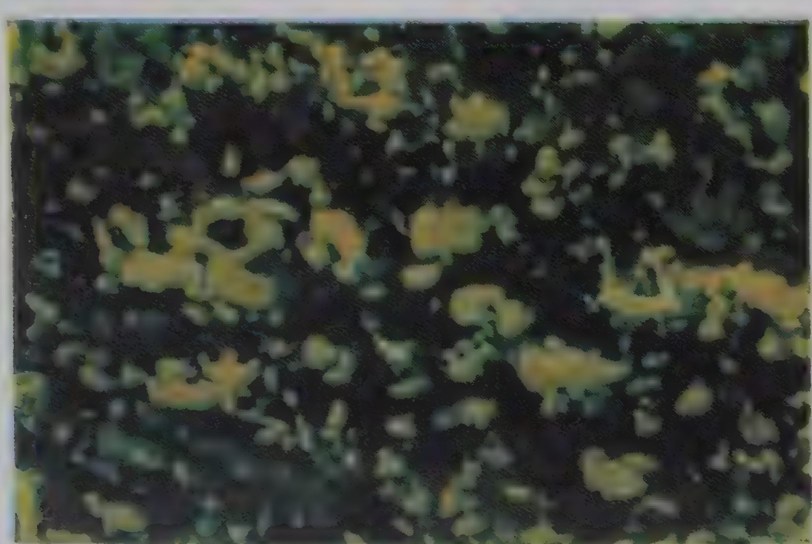


Fig 3. Section of human leproma (treated patient).
(a) Cryostat section, Auramine stain : numerous bacilli and few globi — × 215



(b) Cryostat section. Auramine stain after toluol treatment: few bacilli remain visible — × 215



(c) Section after paraffin embedding, Auramine stain after deparaffinization according to Wade-Fite: numerous bacılli and globi— × 215

Reich et al. (1972) having done a quantitative comparison of standard Ziehl-Neelsen versus Nyka stained smears from leprosy patients, conclude that some leprosy bacilli are chromophobic to the routine Ziehl-Neelsen stain.

We use regularly the Nyka technique for staining smears and tissue sections to detect *M. leprae*, but with some modification of the original method. Instead of a 10% solution of periodic acid, we use a 1% solution and for half an hour only, for smears and tissue sections, with very good results.

FLUOROCHROME STAINING

Fluorochrome staining is generally superior to the Ziehl-Neelsen method, but is not in common use to detect *M. leprae*, perhaps owing to the more expensive microscope needed and to some difficulties in field work.

Lacordaire Lopes de Faria (1974), comparing fluorescent staining with Fite-Faraco procedure, concludes that for tissue sections the Fite-Faraco is superior to auramine and rhodamine staining, but that fluorescent staining gives better results than the Ziehl-Neelsen stain in tissue sections and smears.

We fully agree with this opinion and for smears, in our experience, the fluorochrome procedure is definitely superior to the Ziehl-Neelsen method. However for tissue sections the fluorochrome staining can be improved to give same results as the Fite-Faraco or Wade-Fite procedures. By deparaffinizing tissue sections with a mixture of turpentine and paraffin oil, instead of toluol, prior to auramine staining, same results are obtained as with the complete Wade-Fite procedure.

The detail of our procedure for tissue sections is as follows:

The two first steps are same as in Wade-Fite method.

1. Auramine 0.1 gr.
   stain 15 minutes
   Phenol 5% solution 100 ml.

Auramine is dissolved by aid of a magnetic stirrer and the solution is filtered before use.

2. Wash in tap water
3. Decolorize with 0.5 % HCl in 70% alcohol
4. Wash in water
5. Treat for 20 seconds with 0.1% aqueous solution of potassium permanganate or counterstain with Evan's blue, 0.1% aqueous soln. for 5 minutes,
6. Wash in water and mount in buffered glycerol (glycerol 9 volumes+1 volume phosphate buffered saline).

Slides are preferably examined immediately on fluorescent microscope, or within a few hours, and in the mean time preserved in the dark.

Smears, after fixation, are similarly stained and examined in buffered glycerol immersion.

RELATIVE VALUE AND SIGNIFICANCE OF DIFFERENT STAINING TECHNIQUES

All bacilli stainable with Ziehl-Neelsen are also stainable with Nyka, Wade-Fite, Auramine and Gram methods.

Gram stain is not suitable to detect *M. leprae* in smears and is not commonly used for staining tissue sections, where *M. leprae* are however easily recognizable.

Ziehl-Neelsen is a reliable method for smears and tissue sections, but only for non-treated lepromatous patients, where however more bacilli are often detectable with Auramine, Nyka and Wade-Fite methods.

Before becoming acid-alcohol-fast and stainable with Ziehl-Neelsen, bacilli are already detectable with Nyka, Gram and Wade-Fite.

Bacilli stainable with Nyka, but not yet with Ziehl-Neelsen, do contain polysaccharidic substances also detectable with Schiff's method. When in treated patients bacilli are no more stainable with Ziehl-Neelsen and Nyka, polysaccharidic substances are also no more detectable.

Wade-Fite method is not suitable for smears but is the most reliable method for tissue sections, where however same results are obtainable with auramine staining after deparaffinization with turpentine and paraffin oil.

In borderline cases Ziehl-Neelsen and auramine detects more or less bacilli but no globi. With Wade-Fite, Auramine after deparaffinization according to Wade-Fite and Nyka, much more bacilli and globi become visible and then polysaccharidic substances are stainable with Schiff's method. Sometimes with

Ziehl-Neelsen method non acid-fast bacilli, morphologically similar to the diphtheroid bacilli isolated from leprosy patients, are also visible.

In tuberculoid and indeterminate lesions Ziehl-Neelsen method fails very often to detect *M. leprae*, even in non-treated patients. More or less numerous bacilli are however detectable with Wade-Fite, Auramine after deparaffinization according to Wade-Fite or Nyka methods, and polysaccharidic substances are also visible with Schiff's method.

Following treatment, bacilli stainable with Ziehl-Neelsen and Nyka staining are progressively reduced but maintain for some time their stainability with Wade-Fite, Auramine and Gram's.

The difference between the different staining methods is most obvious in borderline and tuberculoid biopsies. No or only few bacilli being detectable after Ziehl-Neelsen staining, tissue sections may be stuffed with bacilli after Wade-Fite, Nyka, Auramine or Gram staining. These bacilli are also detectable by immunofluorescence with anti *M. leprae* or anti-diphtheroid sera (sera prepared against diphtheroid strains isolated from leprous material).

One may conclude that Ziehl-Neelsen staining is not a sufficiently accurate or sensitive method to detect *M. leprae* and consequently may not be the only oriterion to decide that a patient is no more contagious or need to stop treatment.

In practice Wade-Fite or other variants of Fite-Faraco seems the most suitable and reliable methods to detect *M. leprae* in tissue sections, and for smears, Nyka and Auramine methods.

When bacilli are detectable in leprosy lesions whatever the method used, they are always visible with immunofluorescent technique using either anti *M. leprae* or anti Diphtheroid sera.

LOSS OF ACID-FASTNESS

Fisher and Barksdale (1971) reported the elimination of the acid-fastness but not the Gram positivity of leprosy bacilli after extraction with pyridine. This has been confirmed by Convit and Pinardi (1975) and by us (1975) and is generally considered as specific for *M. leprae*, other Mycobacteria being not affected after such treatment. However acid-fastness is not definitely lost after pyridine treatment and can be restored at least partially when stained with Wade-Fite or Nyka methods.

Acid-Fastness may also be lost after toluol or xylene treatment, and this explains the difference sometimes observed between fresh smears and tissue sections from same biopsy. This is especially demonstrative in leproma from treated patients where the Ziehl-Neelsen staining may detect numerous acid-fast bacteria and globi in smears and cryostat tissue sections, but only few, if at all, in tissue sections from paraffin embedded blocks from same biopsy. After paraffin embedding, bacilli are however still present and demonstrable with Wade-Fite, Gram and Nyka stains. But Nyka method does not always stain as such bacilli as Wade-Fite. Disintegrating bacilli, especially consequent to treatment, may be no more stainable either with Ziehl-Neelsen or Nyka methods.

In non-treated lepromatous patients toluol does not removed acid-fastness and no striking differences are observed between smears and tissue sections stained with Ziehl-Neelsen method, but more bacilli may be detected after Nyka staining. This becomes especially obvious when different staining techniques are applied to serial sections or by staining same section successively with different methods. Nyka after Ziehl-Neelsen or Auramine, or Schiff, or Ziehl-Neelsen after Auramine or immunofluorescent technique are most appropriate for successive staining.

Toluol and pyridine susceptibility of *M. leproe* are not completely assimilable. All *M. leprae*, either from treated or non treated leprosy patients loss their acid-fastness after pyridine treatment, whereas toluol removes the acid-fastness from bacilli only from treated lepromatous patients, and perhaps from tuberculoid and some borderline cases at least partially.

ACID-FASTNESS OF *M. LEPRAE* IN MICE FOOT-PAD

M. leprae adapted to mice foot-pad are stainable with Ziehl-Neelsen method in smears but not at all in tissue sections. This is generally attributed to the decalcification procedure. This is however not the genuine reason, but bacilli in mice are toluol dependent. In sections of the soft tissue of infected mice foot-pad, embedded in paraffin without decalcification, bacilli are no more stainable

with Ziehl-Neelsen but are detectable with Nyka, Wade-Fite or Gram methods.

In smears much more bacilli are detected after Auramine staining.

In recently inoculated mice with bacilli from fresh human leproma, bacili remain stainable with Ziehl-Neelsen method in tissue sections, but after disappearance of the inoculum and active multiplication of *M. leprae* they lose their Ziehl-Neelsen acid-fastness in classical tissue sections, toluol-fastness being completely lost.

The particular behaviour of *M. leprae* in mice may probably be ascribed to a particular specific property of mice histiocytes or cellular immunity, which impedes the development of a lepromatous type of infection.

CONCLUSION AND DISCUSSION

All our observations lead to conclude that *M. leprae* must be a dimorphous organism, existing in a nonacid-fast and an acid-fast stage.

Dimorphism is a well known feature in mycology and it was not without relevance that outstanding mycologists had been invited at the LWM-AFIP CONFERENCE ON RESEARCH PROBLEMS IN LEPROSY in 1965, where the cultivation problem was a particular goal.

What is the relation between the non acid-fast and the acid-fast bacilli in leprosy patients? Are the non acid-fast bacilli precursors or degenerating forms of the acid-fast bacilli, or are they completely different organisms?

One must distinguish between two types of non acid-fast bacteria; those which are and those which are not stainable with Nyka staining, i.e. those which contain polysaccharidic substances and those devoid of such material. In our opinion, resulting from our numerous observations, the non acid-fast bacilli containing polysaccharidic substances are precursors of the acid-fast forms, whereas those devoid of such material are degenerating bacilli having lost their acid-fastness

All these bacilli, acid-fast and non acid-fast, react in immunofluorescence with sera prepared against 'Diphtheroid' like strains isolated from leprosy patients and with anti *M. leprae* serum.

Acid-fast bacilli, nondistinguishible from *M. leprae*, can, though not regularly, be observed in foot-pad of mice and in human macrophages inoculated with Diphtheroid strains. Most human beings in contact with leprosy patients do indeed no more develop the disease.

Rabbits immunized with Diphtheroid strains and tested with lepromin develop a late Mitsuda type response.

Consequently a relation between the diphtheroids isolated from leprosy patients and *M. leprae* may be postulated (Chatterjee, 1976).

Multiplication of acid-fast forms of *M. leprae* may be host dependent, whereas non acid-fast (supposedly precursor) forms could have an autonomous metabolism and consequently able to grow in vitro.

One may not be deliberately unaware of the problem of the so called 'Diphtheroids', which are the most frequently isolated strains from leprosy patients and can also be recovered from inoculated mice, even if we have not yet experimental proof that the diphtheroids could represent a phase in the developmental cycle of the causative organims of leprosy.

In the mean time the 'Diphtheroids' are already very useful in sero-diagnosis. Exhibiting very high sensitivity in immunofluorescence and needing no special treatment they prevail over *M. leprae* or other Mycocacterial antigens.

The hypothesis of a developmental cycle in the causative agent of leprosy could provide an explanation of the clinical and histopathological evolution of certain leprosy lesions.

In indeterminate and tuberculoid leprosy in which leprosy bacilli are scanty or apparently absent, the causative organisms may be present, but in a transitional form. The non acid-fast forms may be more vulnerable and more easily destroyed by the cellular reaction of the host. They can acquire acid-fastness only as a result of a failure of the defence mechanism of the host, which is the case in lepromatous and some kind of borderline leprosy.

In tuberculoid leprosy, the bacilli cannot, except in a small proportion, acquire acid-fastness. In borderline leprosy, the bacilli acquire this acid-fastness in progressive fashion; and in lepromatous leprosy, there

is still a small proportion of bacilli that has failed to acquire acid-fastness. These may represent the vegetative form that is capable of rapid multiplication in vivo and perhaps of growth in vitro.

The abacillary and paucibacillary lesions that transform in a relatively short time into lesions that are crammed full of acid-fast bacilli, are only with difficulty explicable in terms of a generation time of 10 to 15 days. With such a generation time, an increase of 6 logarithmic units would need 8-10 months, a supposition incompatible with the rapid appearance of florid lesions full of acid-fast bacilli; on the other hand, if the transformation of non acid-fast organisms into acid-fast organisms can be the result of a failure in the defence mechanism of the host, this observation can be perfectly explained.

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MYCOBACTERIUM LEPRAE IN THE BLOOD

DAVID J. DRUTZ, AND AUDIE L. MURPHY

INTRODUCTION

Leprosy is a systemic infectious disease. This is particularly obvious toward the lepromatous end of the spectrum where diffuse and symmetrical involvement of skin, nerves, and skin adnexa, and heavy bacillary seeding of reticuloendothelial tissues suggest strongly the hematogenous dissemination of *Mycobacterium leprae*. The systemic nature of leprosy is less readily apparent at the tuberculoid pole of the spectrum where no more than one or two asymmetric paucibacillary neurocutaneous lesions occur. Nevertheless, leprosy bacilli may be found in clinically normal nerves remote from sites of obvious disease (1); other nerves may show histologic abnormalities without bacilli (2); and the liver may be the site of apparent miliary granulomata (3-5). Hence it seems likely that tuberculoid leprosy may be more widespread than its obvious clinical manifestations suggest, and may be preceded by a stage of hematogenous dissemination.

Presently, there is considerable interest in the possibility that leprosy may be spread by the respiratory route from the nasal mucosa of patients with advanced lepromatous disease (6-8). In a susceptible contact, leprosy bacilli might replicate transiently in alveolar macrophages and/or spread by the pulmonary lymphatics to the bloodstream. Such a sequence of events would be entirely comparable to the situation in tuberculosis, where a primary silent bacteremia is quite common (9). The subsequent fate of hematogenously disseminated *M. leprae* would then depend upon the intrinsic immunity of the host to this microorganism. In the majority of contacts, clinical illness might not occur. In others, a vigorous host response might restrict infection to a limited number of foci, with tuberculoid or near-tuberculoid leprosy being the result. In some patients, total failure of host defenses might result in disseminated infection at the outset with a resulting picture of lepromatous leprosy. (It should be noted, of course, that a primary silent bacteremia could occur even if the site of introduction of *M. leprae* into the body should prove to be the skin, rather than the lung (10).

It is currently impossible to study a postulated primary leprosy bacteremia in man in the absence of criteria for establishing the diagnosis at an extremely early stage of infection, and without a technique for cultivating *M. lrprae in vitro*. That *M. leprae* may spread hematogenously from cutaneous or respiratory sites of primary infection has been established unequivocally, however, in thymectomized and irradiated mice (7, 11, 12); in thymectotomized and antithymocyte serum-treated rats (13); in armadillos (14, 15); and in normal mice at the extremes of their lifespan (16).

The purpose of this communication is to discuss not "primary" leprosy bacteremia, but the bacteremia which is associated with leprosy infection which has become advanced and clinically apparent. In a sense, such bacteremia represents a secondary invasion of the bloodstream, comparable, perhaps, to that occurring in hematogenous infection by *Staphylococcus aureus*.

HISTORICAL ASPECTS

Leprosy bacteremia was an object of intense investigation at the turn of the 20th century ; some 80 articles concerning this subject were published between 1890 and 1916 (17-21).* The impetus for investigation of leprosy bacteremia could be attributed to three areas of concern :

(a) search for an explanation for visceral/ systemic involvement in advanced infection ;

(b) evaluation of the possibility of transsplacental transmission of bloodborne

* Early studies are reviewed in references 19-21.

M. leprae (the communicable versus hereditary transmission of leprosy issue being a highly contested one at this time);

(c) evaluation of the possibility of transmission of the disease by biting, blood-sucking insects.

Although many of the early studies of leprosy bacteremia did report the presence of bacilli in smears of the blood (especially during "lepra reactions" or "febrile eruption periods"), these studies were criticized by later workers on the grounds that they failed to differentiate bacilli which may have contaminated blood smears through puncture of involved skin from bacilli which were truly blood-borne (21). The additional possibility that acid-fast bacilli (AFB) in the blood might represent extrinsic contaminants from reagents used in the preparation of blood smears was investigated by Crow in 1912 (18). By the use of autoclaved, double glass-distilled water, concentrated nitric acid washes of glassware, and cultivation of all reagents, he concluded that AFB were present intrinsically in the blood of leprosy patients. The bacilli were found most easily in patients with the "rapidly progressive tubercular* type" of leprosy. In relation to the possibility of contamination of blood from AFB in the skin, he commented : "To my mind, the greatest possibility of contamination was from the skin in inserting the needle when blood is drawn." He attempted to compensate for this, however, by selecting healthy areas of skin for the drawing of blood.

In 1916 Hollmann carried out similar studies, but also directly examined the site of venipuncture for cutaneous AFB (20). In all cases, blood had been drawn from "an apparently healthy portion of the skin." In five of six bacteremic leprosy patients, AFB were present in the skin at the site of venipuncture ; in the sixth, AFB were present only in the blood. Unfortunately, Hollmann failed to indicate clearly whether he considered the bacteria in the blood to represent contaminants from the skin, or whether (as indeed seems to be the case), he considered bacteria found in smears of the apparently normal skin of the venipuncture site to represent contaminants deposited there from the blood.

The topic lay in an ambiguous state until 1933, when Dr. John Lowe published an important paper in The Indian Medical Gazette (21) which established the following points :

(a) thick smears of the blood of the finger tip, prepared in the manner of a malaria smear, are often falsely positive since they reflect the presence of leprosy bacilli in the tissues of the finger tip ;

(b) in blood obtained by venipuncture, it is impossible to identify (and thus avoid) infected skin by observation alone. In the words of lowe : "We have seen dozens of 'normal' areas of skin in which millions of acid-fast bacilli could be found";

(c) even venous blood obtained from apparently healthy skin at the antecubital fossa is subject to contamination by *M. leprae*, although perhaps less so than finger tip blood. (Thus, 24 of 24 patients with positive AFB smears from finger tip blood had positive finger-tip skin smears for AFB, whereas only 15 of 21 patients with positive smears from venipuncture blood had positive skin smears for AFB at the venipuncture site.).

(d) bacillemia is more likely to be present in cutaneous (lepromatous) than in neural (tuberculoid) leprosy. (Blood smears were positive in 15 of 21 patients with cutaneous leprosy, but in only two of 23 with neural leprosy.)

(e) identification of leprosy bacilli in the blood is extremely complicated and is not necessary for the diagnosis of leprosy.

In 1936, Mostert investigated leprosy bacillemia by a method employing preparation of a thick smear from venous blood which was de-hemoglobinized with tap water (23). Recognizing the problem of potential skin contamination of blood smears, he injected 0.5 ml of normal saline to clear the venipuncture needle before obtaining his blood specimen. Considering that extracellular bacilli were most likely to represent contaminants from the skin, he accepted the occurrence of true bacteremia only in patients in whom bacilli were visible in cells of the peripheral blood. Under these circumstances 15 of 15 patients with "nodular" leprosy were found to have bacillemia. He concluded that "bacillaemia is therefore the rule in nodular leprosy and not only the case during acute exacerbations of the disease." Of the blood cells which contained bacilli, 80% were large mononuclears; 3% were small mononuclears; and 17% were polymorphs. In one instance

* i.e., lepromatous leprosy [22].

a gaint cell with a pale eccentric kidney shaped nucleus was found to be packed with bacilli. Bacilli contained in the cells were noted to vary greatly in morphology, but a number were said to be straight, well-formed rods.

Mostert also studied the occurrence of bacteremia in five patients with nodular leprosy and "acute exacerbation." All five patients were bacteremic and the outstanding feature in all was the abundance of intracellular and extracellular bacilli encountered. Again, 80% of the bacilli were in large mononuclear cells.

It is apparent that Mostert anticipated many of the findings that were to be reported in studies of leprosy bacteremia four decades later. It is of particular interest that this author's work is seldom, if ever, referenced in subsequent literature, which has led to his perceptive investigations having been overlooked by many workers, myself included (24).

Studies providing further real insight into leprosy bacteremia were nonexistent until 1941 when Dr. George Fite published a most important paper entitled, "The Vascular Lesions of Leprosy" (25). In a histopathologic study of 77 cases of leprosy he concluded that :

(a) there is vascular involvement in nearly every severe case of the disease (Particularly nodular and "mixed" forms);

(b) vascular involvement is not present at the start of a lesion, but occurs only as lesions age and achieve chronic activity ;

(c) *M. leprae* involves not capillaries alone, but entire terminal vascular loops consisting of arterioles, capillaries, and venules. The bacilli are located most prominently in endothelial cells ; however, intima, media, and adventitia may all be involved ;

(d) pericapillary bacillary infiltrates are commonly encountered, particularly at the margins of active foci, and may constitute one of the important paths by which infiltrations and nodules enlarge in size ;

(e) larger arteries and veins may be involved by direct spread of bacilli in the vascular endothelium ;

(f) still larger vessels may become infected via passage of microorganisms through vasa vasorum ;

(g) based upon these observations he postulated that there would be "a continual discharge of variable degree" of bacilli from the endothelial cells of infected veins into the circulating blood. He supported this contention by observing the presence of heavy bacillary seeding of Kupffer cells and "splenic pulp cells" independent of the occurrence of miliary parenchymal lepromata. Fite concluded that "the vascular infection effects a continuous intravenous autoinoculation of lepra bacilli."

In 1963 Rhodes-Jones carried out a study of leprosy bacteremia using thick smears of venous blood (26). This study differed from others in its attempt to relate the occurrence of bacteremia to clinical subtypes of leprosy. *M. leprae* were present in the blood of 26 of 59 lepromatous, four of 22 tuberculoid, four of seven borderline, five of nine dimorphous, and zero of four indeterminate cases of leprosy. The only precaution which was observed to prevent cutaneous contamination of the blood specimen, however, was surgical exposure of the vein prior to venipuncture in two patients. The blood was positive in both cases. It is, therefore, impossible to rule out entirely the possibility of contamination in other cases.

Taken together, the above studies would suggest that bacteremia is an integral occurrence in advanced cases of leprosy, and that endothelial and pericapillary spread of leprosy bacilli together with frank hematogenous dissemination of microorganisms might explain the widespread nature of lepromatous disease. What is remarkable is that standard authoritative works on leprosy have taken little substantial notice of these observations (27-29). In infectious diseases in general, invasion of the peripheral blood is a dramatic and highly significant event which reflects the breakdown of local host defense mechanisms. Conversely, disappearance of microorganisms from the blood has major significance, suggesting that the host has, often with the help of antimicrobial agents, gained the upper hand in the host-parasite interaction. Failure of bacteremia to clear in the face of an appropriate therapeutic regimen has serious diagnostic and prognostic implications. Generally the occurrence of bacteremia has life-threatening implications ; these clearly do not apply in leprosy. Presumably this is the reason that documentation of leprosy bacteremia had not excited more comment in earlier standard works on leprosy.

MORE RECENT STUDIES

In light of the absence from the general medical literature of any significant commentary regarding the occurrence of leprosy bacteremia or its likely role in dissemination of the disease, it was inevitable that many studies would be repeated by investigators unaware of previously published data. Such has continued to be the case over the past two decades. Some of the studies conducted by my own group are also subject to this criticism, as will become apparent.

Approximately 10 years ago I had the good fortune to be assigned for two years' military duty to the United States Naval Research Unit No. 2 (NAMRU-2) in Taipei, Taiwan. I had just completed training in general internal medicine followed by a two-year fellowship in Infectious Diseases in the laboratory of Drs. David Rogers and M. Glenn Koenig at Vanderbilt University School of Medicine in Nashville, Tennessee. A major interest of that laboratory was reticuloendothelial bloodstream clearance mechanisms. Hence, I had come to Taiwan prepared to study reticuloendothelial function in pertinent diseases of Southeast Asia. I had never before seen a case of leprosy, but was intrigued by studies of the immunology of leprosy published by Dr. Ward E. Bullock, one of my predecessors at NAMRU-2 (30). During this time, Drs. Wen-Hsiang Lu, Thomas Chen and I became interested in the visceral manifestations of advanced leprosy. We were surprised to find few published data pertaining to clinical aspects of leprosy bacteremia or the relation of the bacteremia to visceral lesions. As a result, a series of studies devoted to evaluation of the clinical aspects and accompaniments of *M. leprae* bacteremia was begun.

The techniques employed were relatively simple and familiar ones: thorough clinical and histologic evaluation of patients according to the 5-part Ridley-Jopling classification (31); slit smears of the skin with calculation of bacterial indices and solid ratios (32); multiple skin biopsies; Dharmendra and Mitsuda skin testing (33); careful documentation of any associated disease, infectious or otherwise, which might influence interpretation of data obtained; needle biopsies of pertinent organs (liver and bone marrow; sometimes kidney) to evaluate extent of systemic infection; and use of appropriate laboratory procedures to identify subtle biochemical abnormalities which might shed light upon the consequences of hematogenous infection. In the absence of techniques for culturing the blood for *M. leprae*, smears of the buffy-coat (leukocyte cream) were prepared (34). *Figure* 1

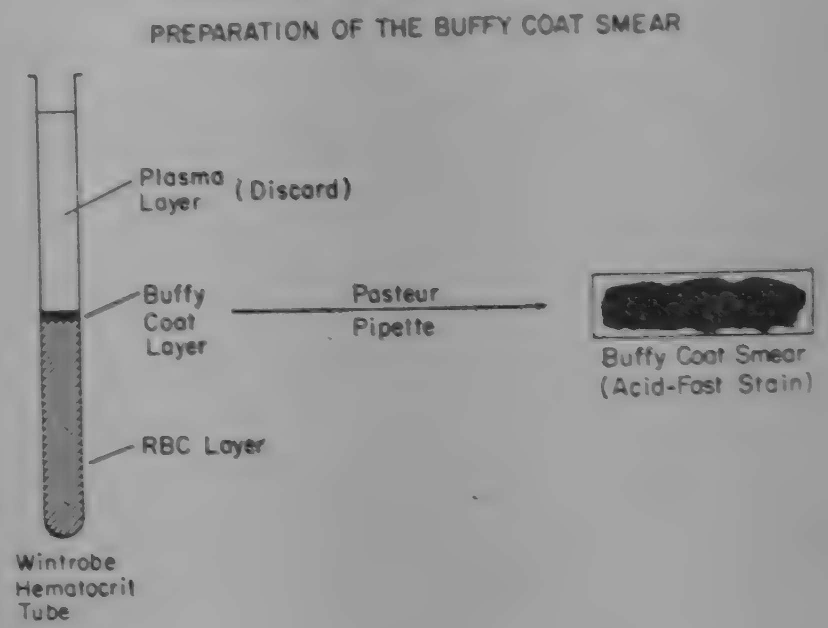

Fig. 1. Preparation of the buffy-coat smear. Heparinized blood was centrifuged in Wintrobe hematocrit tubes, and smears of the buffycoat were prepared, stained with the Ziehl-Neelsen method, scanned for 30 minutes by one technician, and graded semiquantitatively according to the frequency witn which bacilli were encountered. The entire buffy coat from 3 ml of blood was examined.

illustrates how this material was processed. Blood was obtained by venipuncture at the anticubital fossa. The first 5 ml. of blood were discarded in order to eliminate any possibility of contaminants from the skin; the next 3 ml. were obtained in a fresh heparin-containing syringe. In a number of studies, a six inch long polyethylene catheter was passed into the vein and specimens were obtained serially which were clearly free of any cutaneous contamination.

The results of studies on 32 patients are summarized in *Table* 1. Acidfast bacilli were demonstrable in the blood of 25 of 32 patients, whereas control smears prepared from the blood of eight normal control subjects were repeatedly negative. In general, the frequency and intensity of bacteremia correlated closely with the type of leprosy, the BI of the skin, and the duration of therapy. Bacteremia was most pronounced in six patients with previously untreated LL leprosy. In four of these patients (mean BI, 5.9), AFB were present in every buffy-coat smear and were so numerous as to be immediately apparent in scanning at a magnification of 480 times. Two of three patients with LL leprosy who had taken DDS for two to three months (BI's of 6.0 and 5.9) also had strongly positive buffy-coat smears on every occasion.

In patients with LL leprosy and erythema nodosum leprosum (ENL), bacteremia was less frequent and less intense than in otherwise comparable patients with uncomplicated LL leprosy. Thus, three untreated patients with ENL had a few AFB demonstrable in only 54% of buffy-coat smears despite concentrations of AFB in the skin identical (although with fewer solid-staining bacilli) to those of the four patients with untreated LL leprosy and intense bacteremia. We considered the sparse bacteremia to reflect accurately the decline in bacillary viability which apparently predisposes to ENL (35).

A more thorough search was required to locate AFB in buffy-coat smears from LL patients who had been treated for more than one year. Such bacteria were sparse. Nevertheless, the detection of bacteremia in patients who had apparently received effective therapy for this period of time was most impressive.

Four of five patients with BL or BB leprosy were bacteremic. Further, four of seven patients with BT leprosy also had very rare AFB in buffy-coat smears despite the apparent absence of AFB from skin biopsies and smears of tissue fluid. These bacilli may have been artefacts, but it is more likely that biopsies and slit smears were not obtained from involved areas of the skin. (In this respect the buffy-coat smear may be used to real advantage, for it essentially "samples" all areas of the body simultaneously.) Furthermore, A BI "0" indicates only that no AFB were seen in 100 microscopic fields; lower concentrations might have been overlooked. These studies suggest that bacteremia is not a phenomenon restricted to LL leprosy, but occurs in a declining degree across the broad spectrum of leprosy.

The repeated demonstration of AFB in the blood of six patients with untreated LL leprosy suggested that leprosy bacilli might be present in their blood continuously. To test this hypothesis, and to eliminate any remaining possibility that buffy-coat smears might be contaminated by AFB from the skin, blood specimens were obtained from three untreated patients with LL leprosy (mean BI, 6.0) every six hours for two days via six inch long indwelling intravenous cannulas. Every single buffy-coat specimen contained numerous AFB. In similar studies of other patients, rare AFB were present on seven of eight occasions in the blood of one LL patient treated for one year (BI, 3.2), and on five of eight occasions in a patient with untreated BL leprosy (BI, 4.3). Only one single AFB was demonstrable in a monocyte in eight sets of blood specimens obtained from one patient who had BB leprosy (BI, 0.9). Extracellular *M. leprae* were encountered frequently in these preparations which were free of any possibility of skin contamination (*Figure 2*). Hence, extracellular AFB do circulate in the blood of patients with leprosy, and do not necessarily reflect contamination of blood specimens from AFB in the skin, as had been suspected by Mostert (23).

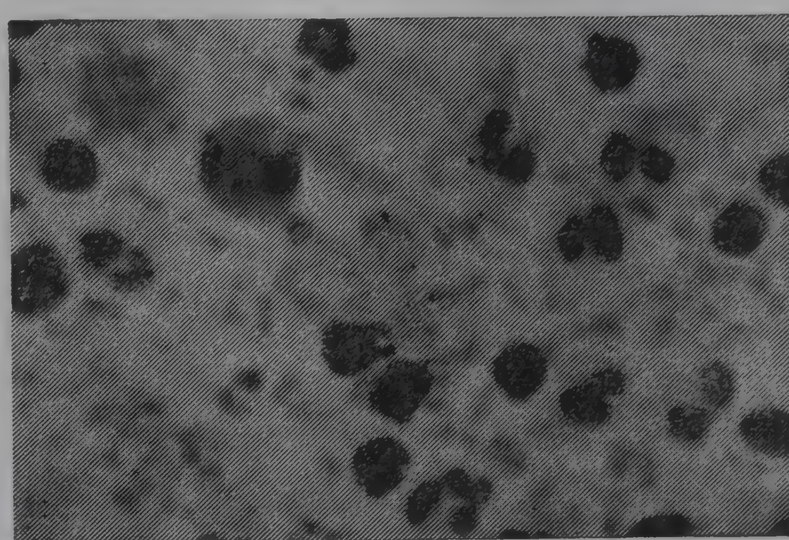

Fig. 2 Extracellular AFB in a smear of the buffy coat from a patient with untreated LL leprosy.

As had been suggested by the work of Mostert (23), AFB were found in polymorphonuclear (PMN) and mononuclear phagocytes (*Figure* 3, a and b ; *Figure 4*, and b). Polymorphonuclears rarely contained more than one to three AFB. There apeared to be two populations of AFB-bearing mononuclear phagocytes: those with one AFB only, and those with 10 or more AFB. The latter cells often had the morphologic appearance of large histiocytes (*Figure* 5). In blood taken from the earlobes of patients with LL leprosy, large numbers of these bacillus-bearing histiocytes were seen. (The microcirculation of the earlobe is a rich source for bacteria-bearing histiocytes in chronic bacteremic conditions such as bacterial endocarditis (36). The distribution of AFB in the mononuclear phagocytes from peripheral blood specimens of three untreated patients with LL leprosy is shown in *Figure* 6.

Bacteremia was quantified by calculating the concentration of AFB-bearing cells in the peripheral blood, correcting for the total and differential white blood cell count, and finally

TABLE 1

INCIDENCE OF BACTEREMIA AND VISCERAL INVOLVEMENT IN PATIENTS WITH LEPROSY

DURING INITIAL THREE-WEEK OBSERVATION

Leprosy Type	Prior Therapy	Total No. of Patients	Bacteremia: No. of Patients	Bacteremia: Positive Smears No.	Bacteremia: Positive Smears %	Intensity of Bacteremia*	Tissue-Fluid Bacterial Index†: Mean	Tissue-Fluid Bacterial Index†: Range	AFB in viscera‡: Liver	AFB in viscera‡: Bone Marrow	AFB in viscera‡: Kidney
LL	None	6	6	58/68	85	3—4+	5.5	4 -6	6/6	2/4	1/2
	DDS, 2-3 mo	3	3	18/24	75	3—4+	5.7	5.2-6	3/3	2/3	0/1
	DDS, 1 yr	1	1	7/10	70	2+	3.2		1/1	1/1	—
	DDS, 5-10 yr	3	2	4/16	25	1+	0.9	0 -1.8	0/2	0/1	0/1
LL; ENL	None	3	3	14/26	54	1—2+	5.9	5.8-6	3/3	2/2	0/2
	DDS, 3-4 yr	2	2	3/19	16	1+	4.0	3.4-4.5	—	—	0/1
	DDS, >10 yr	2	0	0	0	0	2.4	2 -2.8	0/1	0/1	0/2
BL	None	2	2	16/39	41	1—2+	5.2	4.3-6	2/2	2/2	—
BB	None	3	2	5/18	28	1+	1.6	0.9-2.7	1/2	0/1	0/1
BT	None	7	4	6/34	18	1+	0		0/6	0/1	—

* Estimated intensity of bacteremia; 1+, single AFB found after 30.minute search (100 X oil objective, 12X oculars); 4+, numerous AFB immediately apparent in scanning with a 40X objective and 12 X oculars.

† Bacterial index : 1, 1 to 10 AFB per 100 fields (100 X objective, 12 X oculars); 2, 1 to 10 AFB per 10 fields; 3, 1 to 10 AFB per field; 4, 10 to 100 AFB per field; 5, 100 to 1000 AFB per field; 6, more than 1000 AFB per field. Values listed are the means from the six to eight sampled.

‡ Number of positive biopsy specimens/total specimens examined. No patient had more than one biopsy during the period of observation.

Reproduced, with permission, from Drutz, DJ, *et al* : The continuous bacteremia of lepromatous leprosy. N Engl J Med 287:159-164, 1972.

TABLE 2

ACID-FAST BACILLI (AFB) IN LEUKOCYTES OF FIVE PATIENTS WITH LEPROMATOUS LEPROSY AND BACTEREMIA*

Patient	Bacterial Index	Cells (per Cubic Millimeter) Containing AFB†: Polymorphonuclear Leukocytes No.	Polymorphonuclear Leukocytes %‡	Mononuclear Cells No.	Mononuclear Cells %	Total White Cells No.	Total White Cells %	Mean no. of Infected Cells per Milliliter
1	6.0	8	0.2	9	3.0	17	0.3	17×10^3
2	5.7	6	0.3	4	3.0	10	0.2	10×10^3
3	6.0	4	0.2	2	2.0	6	0.2	6×10^3
4	6.0	9	0.2	3	2.0	12	0.2	12×10^3
5	6.0	5	0.1	12	3.0	17	0.3	17×10^3

* Extracellular AFB were also present in every specimen.

† Each value represents the mean of at least three separate specimens taken on different days.

‡ Percentage of respective cell type containing AFB.

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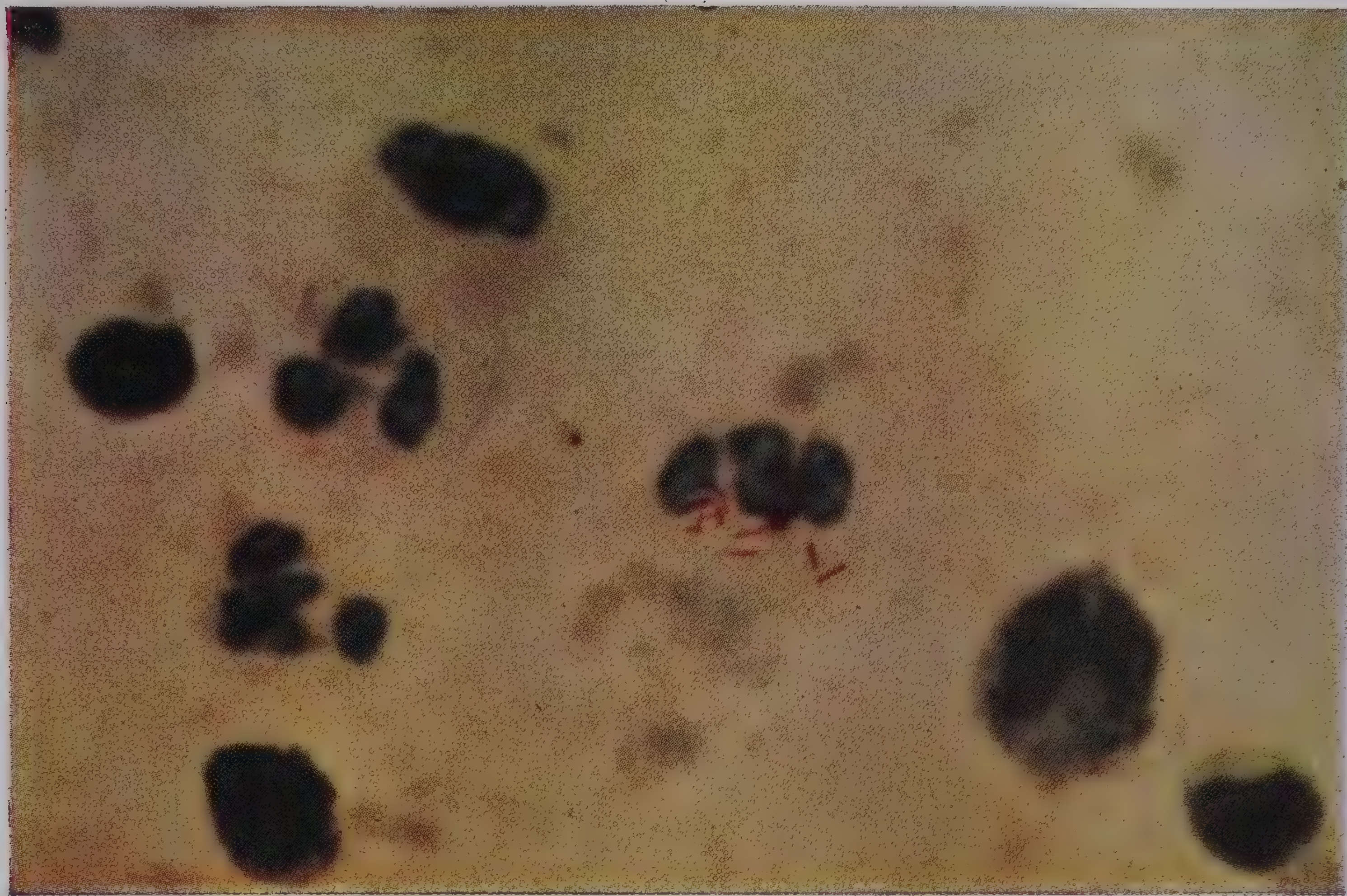


Fig. 3A Polymorphonuclear leukocyte containing more than 10 *M. Leprae*

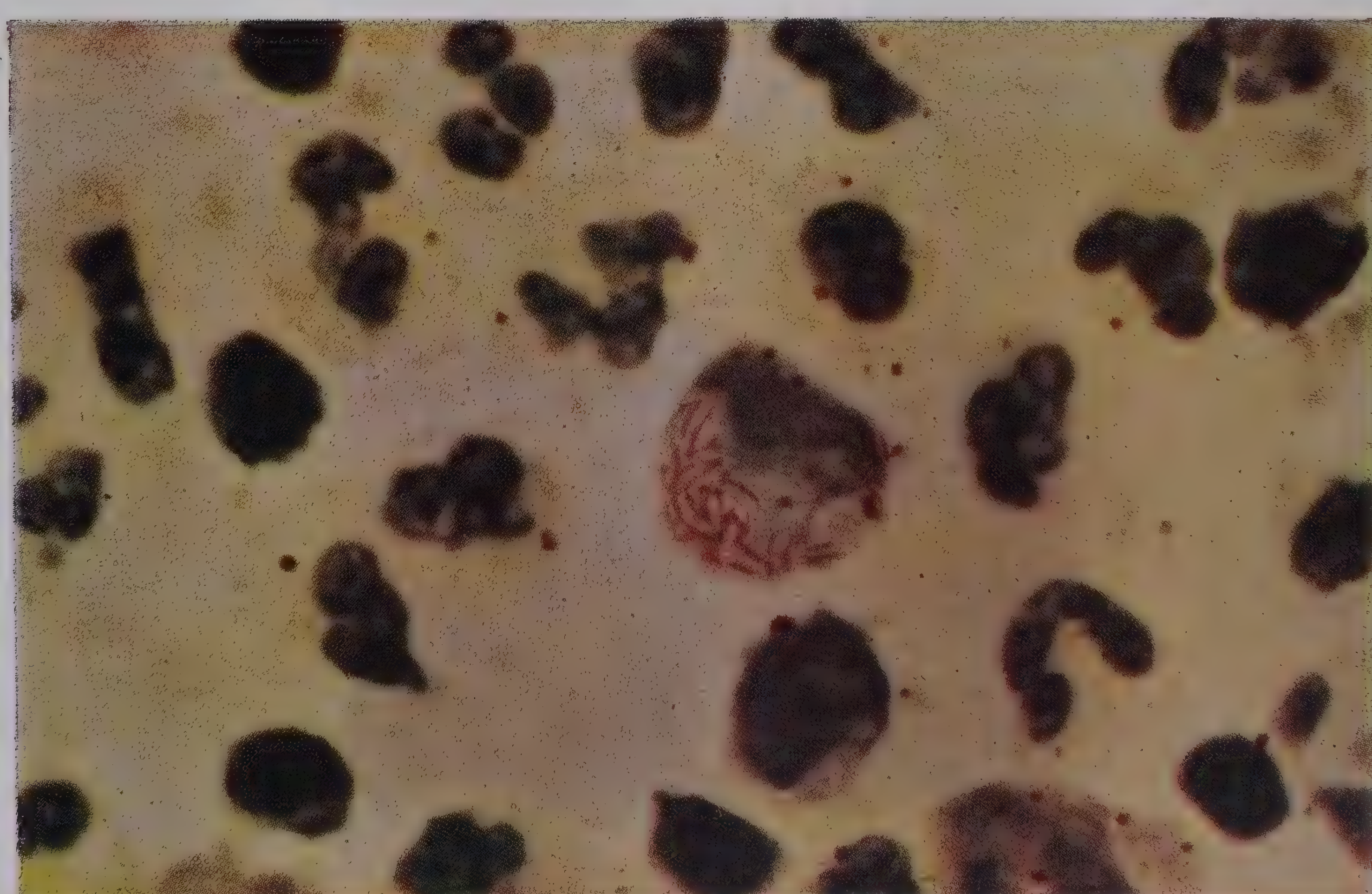
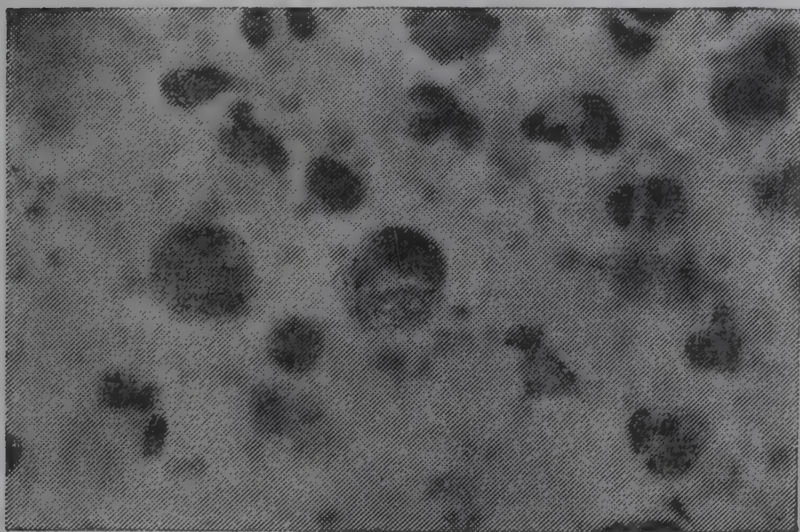


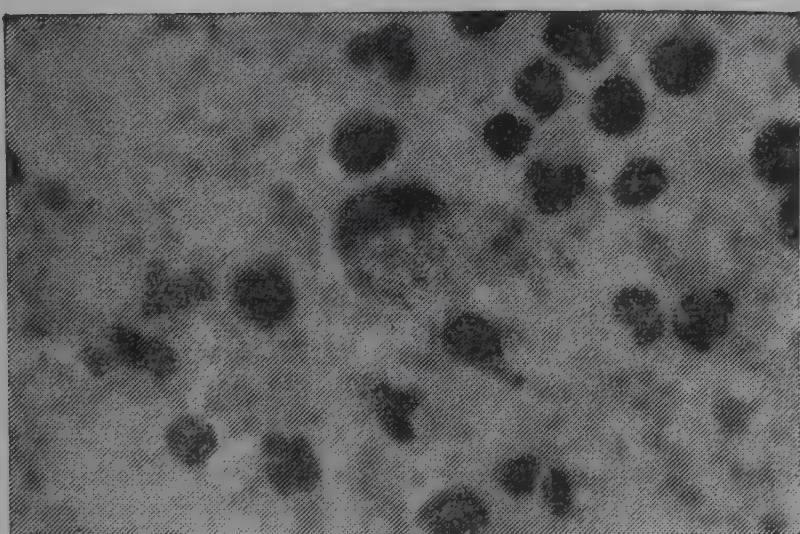
Fig. 3B Monocyte containing a large number of *M. Leprae*

Fig. 7 Vascular invasion by *M. Leprae*-AFB are clearly visible within endothelial cells as well as free within the vessel lumens (fite-faraco stain)

by taking into account the number of AFB found per white cell. The proportion of peripheral blood leukocytes harboring



A



B

Fig. 4. a and b. Mononuclear phagocyte packed with *M. leprae*.

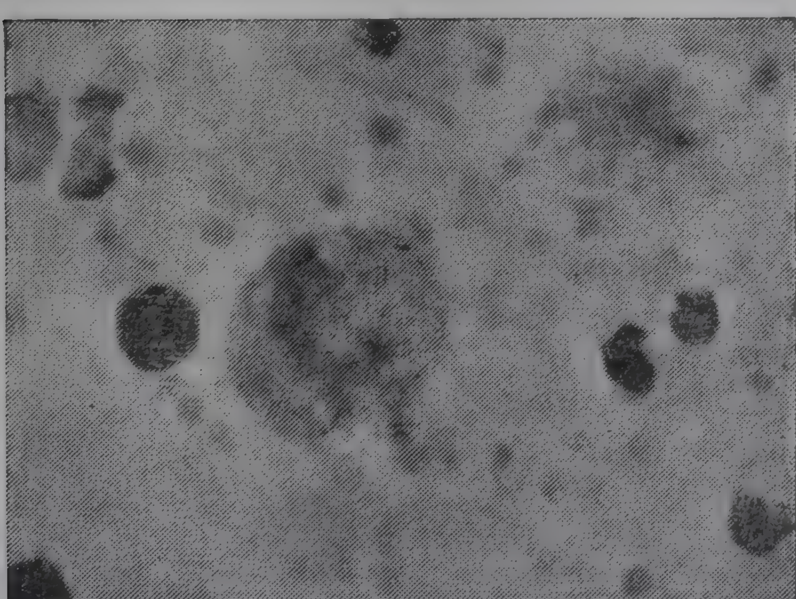


Fig. 5. Mononuclear phagocyte (histiocyte) containing a high concentration of *M. leprae* (reproduced, with permission, from Drutz DJ, *et al:* The continuous bacteremia of lepromatous leprosy. N Engl J Med 287:159-164. 1972).

M. leprae in five patients with LL leprosy and bacteremia is shown in Table 2. Between 0.1 and 0.3 per cent of PMN's and two and three per cent of mononuclear phagocytes contained AFB. Thus, between six and 17×10^3 phagocytes per milliliter of blood contained AFB in these heavily infected patients. Considering that some cells contained up to 10 or more bacilli, and that extracellular AFB were encountered regularly, at least 10^5 AFB per milliliter (or 5×10^8 AFB in a blood volume of 5 liters) were constantly present in the blood of these patients. The general accuracy of our quantitative procedures were subsequently confirmed in an independent study in which AFB were selectively concentrated from preparations of frozen and thawed white blood cells (37).

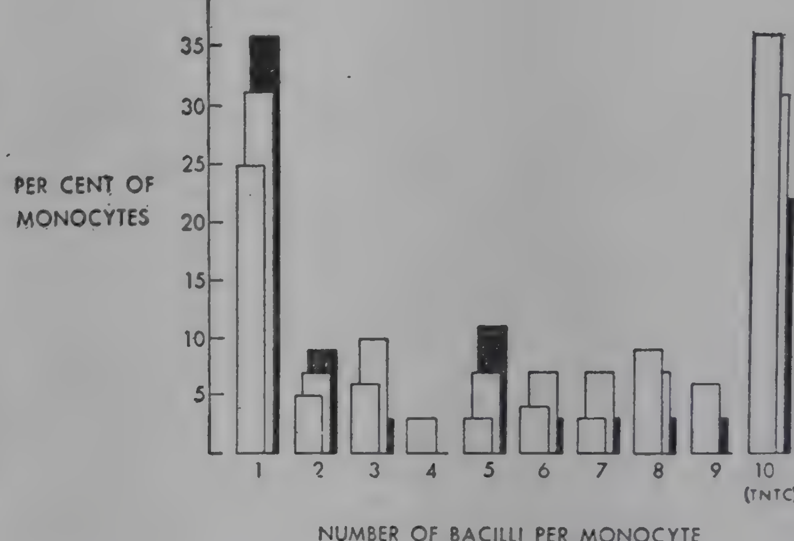


Fig. 6. Distribution of leprosy bacilli in the monocytes of three untreated patients with LL leprosy (reproduced, with permission, from Drutz DJ, *et al:* The continuous bacteremia of lepromatous leprosy. N Engl J Med 287:159-164, 1972).

This is an extraordinary degree of bacteremia, and all the more remarkable for the absence of the usual manifestations of septicemia (i.e., fever, chills, leukocytosis, disseminated intravascular coagulation, etc.). There are few infections in which bacteremia is so intense that micro-organisms can be seen in smears of peripheral blood. In patients infected with *Staphylococcus aureus*, *Streptococcus pyogenes*, *Neisseria meningitidis*, *Clostridium perfringens*, and *Pasteurella* (*Yersinia*) *pestis*, bacteremia of this magnitude has been encountered (34 ; 38-41). Quantitative studies have suggested that when more than 15 infected leukocytes per cubic millimeter are present in smears of blood from the earlobe, patients do not survive (42). Clearly, this is not the case in leprosy.

Simultaneously, studies of arterial and venous blood were conducted with specimens taken from the arms of two patients with untreated LL leprosy; no consistent differences were found in concentrations of bacilli from the two sites. Allowing for inherent inaccuracies of buffy-coat counting methods, these findings suggested that significant numbers of AFB were not entering the blood from infected tissues of the arm. This observation is rather surprising and requires further documentation.

Attempts to determine the solid ratio of bacilli circulating in the blood were frustrated by background staining from leukocyte elements. Even when attempts were made to selectively remove leukocytes by hypotonic lysis, repeated freeze-thawing, or treatment with sodium deoxycholate, bacilli could seldom be purified sufficiently to allow truly critical determination of the solid ratio. In essence, however, although solid-staining AFB were clearly present in the blood, they were outnumbered by AFB which stained irregularly. Since only solid-staining AFB are definitely viable (43), our findings suggested that a majority of *M. leprae* circulating in the blood were dead. This observation may be unique to leprosy. However, other bacteremic diseases have not been investigated in a manner which would permit identification of circulating, but non-viable bacteria. It has been our impression that extracellular AFB in the blood are more likely to be solid-staining than bacilli within leukocytes. We have also noted that extracellular AFB are the first to disappear from the blood following the initiation of chemotherapy (24). Further studies of these issues are clearly in order.

Our studies relative to cutaneous vascular infection by *M. leprae* confirmed precisely the findings of Fite, which have been discussed previously (25). Patients with bacteremia usually had obvious bacillary invasion of arterioles, capillaries, and venules in the skin (*Figure 7*). Ordinarily, vascular invasion occurred in areas in which AFB were present in surrounding tissues. However, AFB were also seen occasionally within the endothelial cells of blood vessels apparently distant from areas of heavy bacillary skin infiltration (*Figure 8*). This phenomenon has been commented upon by Fite (25) and others (2, 44, 45). It is possible that spread of leprosy may therefore take place by direct invasion of vascular endothelium from AFB circulating in the blood.

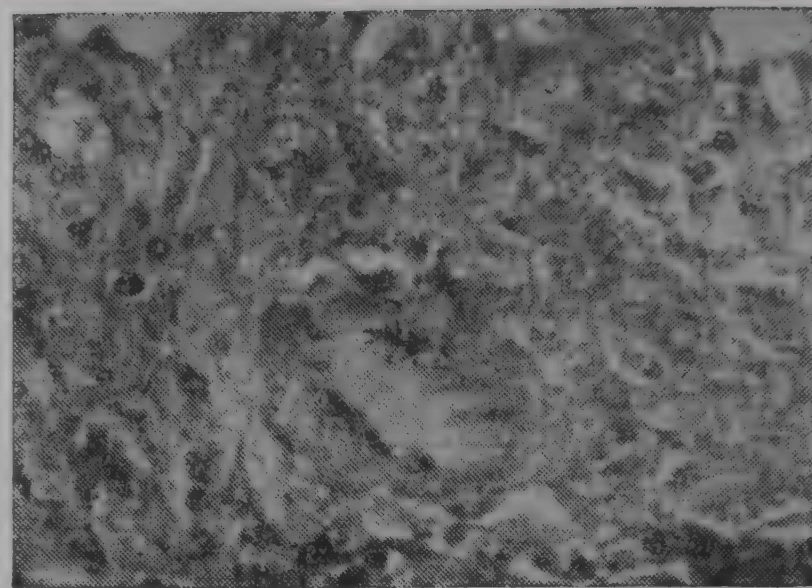


Fig. 8 Apparent isolated endothelial cell invasion by *M. leprae*. Note the paucity of bacilli in the surrounding tissue.

In the patients with continuous bacteremia, there were free AFB identifiable within vascular lumens on histologic sections of skin biopsy material. These could have represented artefactual spread by the microtome knife from contiguous, heavily bacillated skin. However, they were encountered less frequently in treated patients in whom tissue concentrations of bacilli appeared equally high. (Disappearance of free intraluminal AFB from the capillary bed of the nasal mucosa has also been noted in patients who have received dapsone for one year (46). As a result, in untreated patients, the likelihood of bacteremia could often be predicted from the appearance of the skin biopsy. Endothelial cell invasion often remained prominent for some time after treatment had sharply curtailed the bacteremia, however.

As shown in Table 1, AFB were found in 15 of 18 biopsies of the liver and nine of 14 biopsies of the bone marrow in patients with LL and BL leprosy. Although rare AFB were present in the glomerular endothelial cells of one untreated patient with LL leprosy, invasion of the renal parenchyma was not encountered in any of the 10 renal biopsy specimens. Sparing of kidneys by *M. leprae* is well known (47-49); the renal biopsy studies were actually obtained in conjunction with other studies which concerned immunologic complications of leprosy (50, 51).

The appearance of biopsy specimens of the liver correlated particularly well with the presence of bacteremia (52). Whereas intrahepatic parenchymal aggregates of bacillus-bearing macrophages ("lepromata") were common in most patients with high concen-

trations of AFB in the skin, only those who were actively bacteremic also had AFB demonstrable within both hepatic sinusoids and Kupffer cells (24). Fite had noted similar findings in autopsied patients (25).

The presence of AFB within specimens of bone marrow appeared to relate to the presence of active bacteremia (*Table 1*). However, leprosy bacilli located within the marrow were nearly always grossly fragmented; intact micro-organisms were rarely seen. Others have made the same observation (53). Although we did no comparative studies of concentrations, solid ratios, or mouse footpad infectivity of AFB in skin, liver and bone marrow, such studies have been carried out by others (54-56). Reports of solid-staining, footpad-infective *M. leprae* in the liver and bone marrow of lepromatous patients (54, 55) are difficult to interpret since AFB could have been freshly deposited in these tissues by an ongoing bacteremia (55). Recent observations suggest that *M. leprae* may survive in the bone marrow long beyond the time that chemotherapy eliminates footpad-infective AFB from the skin (56). If these observations are corroborated by others, it will bring strong support to the possibility that *M. leprae* may persist and thrive in certain "warm" areas of the body.

Having demonstrated conclusively the occurrence and the magnitude of leprosy bacteremia, it then became necessary to document the viability of *M. leprae* circulating in the blood if the argument for hematogenous spread of leprosy infection were to be resolved unequivocally.

Two types of studies were undertaken. In the first, a novel approach to documenting viable *M. leprae* was utilized in which monolayers of peripheral blood monocytes (and histiocytes) were prepared in tissue culture from the circulating leukocytes of bacteremic LL leprosy patients. Monocytes are glass-adherent and will mature to macrophages in tissue culture. Polymorphonuclear leukocytes are also glass adherent, but die and leave the glass in two to three days. Lymphocytes are not glass adherent. In an LL patient, two to three per cent of circulating monocytes contain *M. leprae*. In tissue culture, such monocytes continue to harbor their *M. leprae* during transformation into macrophages *in vitro*. Leprosy bacilli are still infective for the mouse footpad after three weeks of such intracellular residence *in vitro*, although they do not increase in number (57). In order to assess the viability of the intracellular *M. leprae*, tissue culture tubes were pulsed with tritiated thymidine of high specific activity (18Ci/mM). The rationale was that viable micro-organisms might be synthesizing DNA, even if not actively dividing. The occurrence of bacillary labeling was sought by autoradiography (58). These studies demonstrated labeling of small numbers of *M. leprae*, particularly those occurring in globi, and suggested that at least some of the *M. leprae* circulating in the blood were alive. The ability of *M. leprae* to incorporate tritiated thymidine has since been corroborated by others (59). However, radiolabeling technology for *M. leprae* is still in its infancy (60), and many problems remain to be resolved (61).

A more traditional technique for evaluating the viability of blood-borne *M. leprae* was carried out in collaboration with Dr. Louis Levy and Ms. Sheila M. O'Neill of the Public Health Service Hospital in San Francisco (37). Ten adult patients with untreated LL leprosy were studied. We found 4.48×10^6 to 5.12×10^9 *M. leprae* per gram of skin, and 9.8×10^2 to 1.17×10^5 *M. leprae* per ml. of blood in these patients before they began treatment. Micro-organisms from both sites in all 10 patients were viable as judged by their ability to multiply in the mouse footpad in the manner characteristic for *M. leprae*. Skin-derived bacilli had a relatively uniform incubation period of six to seven months, and an average doubling time of 28.6 to 56.2 days in the footpad. In similar measurements of bacilli recovered from the blood, fluctuations were considerably greater (incubation period five to 12 months; average doubling time 23.4 to 79.9 days), reflecting, at least partly, variations in size of the original inocula.

Neither dapsone (50 mg/day) nor rifampin (600 mg/day) reduced the concentration of AFB in the skin during 16 weeks of study, but both drugs produced a gradual 2 log decline in the level of bacteremia. Within one week after the start of therapy with rifampin, micro-organisms in the skin were no longer infective for the footpad. Micor-organisms obtained from the blood of rifampin-treated patients were not checked for viability until one month after therapy was started. At that time they, too, failed to infect the footpad. In contrast, the skin and blood of dapsone-treated patients contained infective bacilli for four to 16 weeks.

Rifampin, despite its superior antibacterial activity, cleared the bloodstream of bacilli no more rapidly than did dapsone. It remains unclear whether bacteremia in the face of rifampin therapy reflects the release into the circulation of dead *M. leprae*, or whether the mouse footpad technique is insufficiently sensitive to detect a low proportion of viable *M. leprae* which continue to actively invade the bloodstream.

STUDIES FROM OTHER LABORATORIES

In 1972, Manja and his coworkers reported an investigation of leprosy bacteremia which had been undertaken in order to evaluate the possible role of arthropods in the transmission of leprosy (62). A glass adherence method was utilized in which leukocytes in plasma from gravity-sedimented refrigerated blood were allowed to attach to glass slides. Thirty-eight of 38 (100%) untreated lepromatous patients were bacteremic, whereas bacteremia was less frequent in treated patients (14 of 31 patients treated for six months ; four of 12 treated for one year ; and 16 of 70 patients treated for more than one year). Only five of 20 patients with borderline leprosy were demonstrably bacteremic. Of 15 patients with tuberculoid leprosy, none was bacteremic. Most AFB were seen in macrophages ; some were in polymorphonuclear leukocytes (especially among untreated lepromatous patients). In the words of the authors, "in most cases the bacilli were solidly stained and could be counted with ease, even when inside the macrophages." These investigators calculated that 5×10^3 to 5×10^5 AFB were present per ml of blood in their patients. Of 77 samples of blood which were smear-positive for AFB, 15 were inoculated into footpads of mice. At the time the paper was written, multiplication of AFB had occurred in seven cases. In a companion study (63), Narayanan and his coworkers demonstrated the presence of mouse footpad-infective *M. leprae* in bedbugs and mosquitos which had been allowed to feed upon untreated lepromatous patients. The detection in budbugs of bacteria-laden leukocytes suggested to the authors that the insects took up the bacilli along with the blood, rather than from the skin. Whether it is necessary for bacteremia to be pressent in order for a biting insect to ingest *M. leprae* from a patient with highly bacilliferous skin remains unclear, however.

More recently, Padma and Desikan have utilized the buffy-coat smear technique to investigate leprosy bacteremia (64). A double syringe technique was utilized to minimize cutaneous contamination of blood specimens obtained from the antecubital vein. Quantitation of circulating *M. leprae* was carried out by counting the number of microorganisms in a smear prepared from a 5 ul aliquot of leukocyte-rich plasma. Of 114 patients with lepromatous leprosy 77 (68%) showed bacilli in the blood. In 67 of the 77, bacilli were present predominantly in monocytes. In 13 cases, bacilli were also found in PMN's. These investigators found it difficult (as had we) to estimate the ratio of solid to fragmented organisms : "Solid (uniformly staining) bacilli which are believed to be the viable forms were found in varying proportions in 19 cases, while in 48 cases the bacteria were all fragmented. The presence of the presumably viable (uniformly staining) bacilli in blood, supports the possibility that they could settle down in new sites, and produce fresh lesions." In nine of 14 cases in which quantitation of the bacteremia was attempted, the number of bacilli was estimated to be less than 10,000 (i.e., $<10^4$) per milliliter of blood. No correlation was found between the density of bacilli in the skin and the number in the blood. The reason for this is not clear ; the data stand in clear contrast to our own (24).

There have been numerous additional studies of leprosy bacteremia over the years (65-67); some are quite recent (68-70). None of these has provided additional insight into the problem of bloodstream invasion by *M. leprae*.

REMAINING PROBLEMS

Bacteremia and Reactional Leprosy

It is of particular interest that many early investigators considered leprosy bacteremia to be associated with leprosy exacerbations or "reactions." Although we have shown that ENL is associated with a reduction in bacteremia (as might be expected from the fact that ENL appears to be related to the death of *M. leprae*), there have been no similar studies of bacteremia in borderline (lepra) reactions (71). It seems at least possible that downgrading reactions might be associated with an increased incidence of leprosy bacteremia. This point deserves further investigation.

The Infected Endothelial Cell

Endothelial cell infection by *M. leprae* has been noted since the earliest histopathologic studies of this disease (22, 25). Endothelial cells are not considered to represent elements of the vasculature which engage in bloodstream clearance of particulate material. Indeed, the recent impetus for changing the term "reticuloendothelial system" to the more specific "mononuclear phagocyte system" has come, at least in part, from data suggesting that endothelial cells neither originate from peripheral blood monocytes nor are normally phagocytic (72).

It is well known that bacteria-laden phagocytes may marginate along the walls of blood vessels. It remains to be proven by specific investigative techniques that *M. leprae*-laden "endothelial cells" are not, in fact, merely marginated monocytes or histiocytes. Should endothelial cells prove to be specifically receptive to the growth of *M. leprae*, further investigations of this cell type as a vehicle for tissue cultivation of *M. leprae* should be undertaken. We are currently engaged in such studies in my laboratory.

The Continuous Nature of Leprosy Bacteremia

The continuous presence of microorganisms in the blood is a distinctly uncommon event which generally reflects the occurrence of infection on a vascular surface. The prime clinical example of continuous bacteremia is bacterial endocarditis (73), where it is the valve surface which is infected. Superficially, the continuous nature of leprosy bacteremia is explainable on the basis of the widespread vascular infection which has been discussed. There are, however, alternate potential explanations.

In at least two diseases caused by facultative intracellular bacteria, typhoid fever and brucellosis, persistent bacteremia may occur in the absence of an obvious focus of intravascular infection. In both diseases, and in leprosy, it is possible that persistence of bacteremia relates to the recirculation of bacteria which are contained within cellular elements of the blood, especially monocytes. Since monocytes constitute a portion of the mononuclear phagocyte system, it is possible that microorganisms sequestered in such cells may recirculate, without threat of ingestion by fixed phagocytic cells in the liver, spleen, and bone marrow. This possibility has been raised in studies pertaining to potential intracellular survival of *S. aureus* (74).

Another possibility relates to the phenomenon of "reticuloendothelial blockade." The postulate in this case would be that the macrophages of the mononuclear phagocyte system are so saturated with *M. leprae* that no further phagocytosis is possible. The logical result would be a persistent bacteremia.

It has been demonstrated repeatedly that splanchnic trapping mechanisms are not exhausted in the course of natural infections (75-77). However, in none of the diseases investigated were microorganisms presented to the mononuclear phagocyte system in the numbers and constancy, and for the duration that occurs in lepromatous leprosy. Studies employing radiolabeled, microaggregated human serum albumin have shown a normal or increased rate of bloodstream clearance in patients with lepromatous leprosy (78), but it is clear that bloodstream clearance is a very particle-specific phenomenon (79, 80). What is true for albumin may not be true for *M. leprae*.

In an attempt to determine whether the mononuclear phagocyte system is "blockaded" in lepromatous leprosy, we have counted directly the numbers of AFB in blood from peripheral arteries and veins, the hepatic vein, and the superior and inferior vena cavae of a bacteremic patient with LL leprosy. The concentrations of *M. leprae* in blood from the hepatic vein were not appreciably lower than in other sites. These observations would tend to suggest that leprosy bacilli were not efficiently cleared across the hepatic bed (81). An alternate explanation would be that *M. leprae* proliferating in the Kupffer cells of the liver were released into hepatic vein blood at about the same rate that leprosy bacilli entering the portal circulation were cleared by fixed phagocytic cells of the hepatic sinusoids. It is impossible, on the basis of data currently available, to choose between these alternatives.

The Survival and Replication of *M. leprae* in the Bone Marrow and Liver

Recent observations by Karat suggest that *M. leprae* may survive in the bone marrow long beyond the time that they are killed in the skin (54). A possible explanation for these findings may be that the marrow is serving as an efficient filter for viable AFB which continue to invade the bloodstream in numbers too low to detect by buffy coat or

other blood concentration methods. In this regard, it is well to remember the limitations of footpad technology. The sensitivity of the mouse footpad method is limited by the requirement of a bacillary inocululum of $\geqq 10^4$ m. leprae under these circumstances, observable multiplication of leprosy bacilli will not occur in the footpad when the proportion of viable *M. leprae* (approximately 1 in 10 AFB in the skin of a patient with untreated LL leprosy) has been decreased by treatment to $< 1 : 1000$. Thus, if there are 10^5 viable *M. leprae* in a skin biopsy specimen that contains 10^9 AFB, there will be no measurable multiplication in the footpad of the normal mouse. (Admittedly, thymectomized animals such as those used by Karat may be somewhat more sensitive to infection with inocula of low viability (82).) In patients with advanced LL leprosy, who harbor a total bacillary population of 10^{11} *M. leprae*, footpad inoculation studies would be negative when therapy had reduced the number of viable bacilli to below 10^7. Therefore, leprosy bacteremia may occur beyond the time that footpad infectivity of skin-derived *M. leprae* is lost. Our studies (noted previously) which have evaluated bacteremia in patients who received dapsone or rifampin for 12 to 16 weeks have suggested that this is the case. It appears, in fact, as if very low-level bacteremia may be demonstrable for years after dapsone treatment is begun (24, 62). It is the issue of whether such bacilli tend to accumulate in the bone marrow (or liver) which is a crucial one.

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MYCOBACTERIUM LEPRAE IN THE MOUSE FOOT-PAD

K. V. DESIKAN

The evolution of the mouse foot-pad model, its working details and its application have been discussed in another section. In this section, certain biological features concerning *M. leprae* in the mouse foot-pad will be brought out.

Pattern of multiplication

Normally 5,000 to 10,000 leprosy bacilli are inoculated into each of the hind foot-pads of the mouse. The Swiss Albino mice or the CBA mice are generally used, but several of the known strains of the laboratory bred mice have been found to be useful for these experiments. The inoculated mice are kept in suitable cages and housed in an air-conditioned room. Harvests are done six months after the inoculation, sacrificing mice at monthly intervals to monitor the progress of the infection. It has been found that the pattern of multiplication can be divided into 3 phases. The first phase called the "lag phase" corresponds to the incubation period and there is virtually no multiplication of bacilli during this phase. The second or the "log phase" is a phase of rapid multiplication of bacilli which reaches its peak by about 210 days. The third phase is called the "plateau phase" and during this phase the bacillary number more or less remains constant. During this phase there is simultaneous multiplication and death of bacilli so that there are minor waves of rises and falls in the number of bacilli. Subsequently, there is a slow fall in the bacillary content of the foot-pad.

Histological events

As could be expected, the first cell type that appears at the site of inoculation is the polymorphonuclear leucocyte. During the second week, mononuclear cells composed of small numbers of macrophages and lymphocytes are seen. Subsequently these disappear. The bacilli are found in the connective tissues in the fibroblasts and occasionally in some of the tissue histiocytes. Rees et al (1967) are of the opinion that the bacilli specially get colonized in the striated muscles and the multiplication of the bacilli is confined predominantly to these striated muscles. During the lag phase and early part of the log phase, inflammatory exudate is minimal. At the height of bacillary multiplication, there is a mild infiltration by mononuclear cells. During this phase the number of bacilli tend to fall, but secondary waves of growth follow (Shepard and McRae, 1965).

Effect of room-temperature on bacterial multiplication

Shepard (1965) has worked out the requirements of room temperature for the mouse experiments and has indicated that the optimum temperature for the growth of bacteria in the mouse foot-pad is between 15°C and and 25°C. His experiments have shown that a temperature below 4°C or above 35°C is deterimental to the growth of *M. leprae* in mice. However, it has been reported by Karat (1970) that thermo-regulation is not necessary for bacterial multiplication in the mice and he has claimed satisfactory growth of bacteria in the mouse foot-pads when the animals are lodged in a non-airconditioned room at the tropical temperature in South India. Job (1973) on the other hand has not been able to confirm the multiplication of *M. leprae* without proper thermo-regulation. Desikan (1975) working at Chingleput with and without airconditioning of the Animal House is also of the opinion that proper thermo-regulation and room temperature of 20° to 25°C is essential for the growth of *M. leprae* in the mouse foot-pads. He is of the opinion, based on his own findings, that without proper thermo-regulation, the bacterial growth is slow and inconsistent. There is a much longer incubation period of 8 months or more as against 5 to 6 months with thermo-regulation.

Generation time

With the advent of the mouse foot-pad model, it has been possible to calculate the generation time of *M. leprae*. Desikan (1975) has calculated the generation time under the laboratory conditions at Chingleput. The generation time is calculated on the basis of the multiplication factor as against the time taken for multiplication. The following formula is applied for the calculation of generation time:

$$\text{Generation time (G)} = \frac{t}{\log_2 H/F}$$

where 't' is the time taken for multiplication, 'H' is the number of bacilli harvested and 'F' is the number of bacilli inoculated. Calculated by the above formula, the average generation time was found to be 35 days, with a range of 24 to 47 days. This calculation is based on the assumption that all inoculated bacilli multiply. However, presuming that only solid bacilli are viable as is generally believed, the Generation time G(S) is calculated by the following formula (McRae and Shepard, 1971):

$$G\ (S) = \frac{t}{\log_2 H/Fs}$$

where 'Fs' is the number of solid bacilli in the inoculum. Based on this formula the Generation time G(S) was found to be 19.8 days with a range of 15 to 32 days.

Fate of inoculated organisms in the mouse foot-pad

It has been observed in the very early experiments of Shepard (1960) that there was no multiplication of bacteria during the first 4 months after inoculation. It is of interest therefore to find out the events in the foot-pad during this period particularly in the first 3 months. An investigation to this end was undertaken by Desikan (1975). In his experiments, 7,50,000 leprosy bacilli were inoculated into the mouse foot-pad and harvests were made on these animals after 1 day, 2 days, 3 days, and 1, 2, 3, 4, 6, 8, 10 and 12 weeks after inoculation. The results of the harvests are shown in Fig. 1. It was found that 24 hours after the inoculation only about half the number of bacteria could be recovered from the mouse foot-pad. The recovery fell to 20% at the end of 48 hours. There was a slower fall subsequently. At the end of 8 weeks, there was an extremely small number of bacilli detected in the mouse foot-pad. The possibility of the bacteria leaking out of the foot-pad has also been excluded in parallel experiments. These observations correspond to those of Levy et al (1974). It is not clearly understood as to what really happens to the inoculated bacteria. Levy et al (1974) attempted to locate the organisms lost from foot-pad, but no clue could be obtained. One should also consider the possibility that the inoculated bacilli might be going through various stages of their life cycle (Chatterjee 1965) and the organisms might possibly be devoid of their acid-fast staining so that they are not recognised in the foot-pad material by the usual Ziehl-Neelsen stain. In order to find out this posstbility, the studies of Desikan were extended by which the foot-pad material obtained from inoculated mice found negative for bacteria after 7-8 weeks was passaged to fresh mice. These experiments did not show any bacterial multiplication and failed to demonstrate the occurrence of any viable non-acid-fast *M. leprae* in the mouse foot-pad.

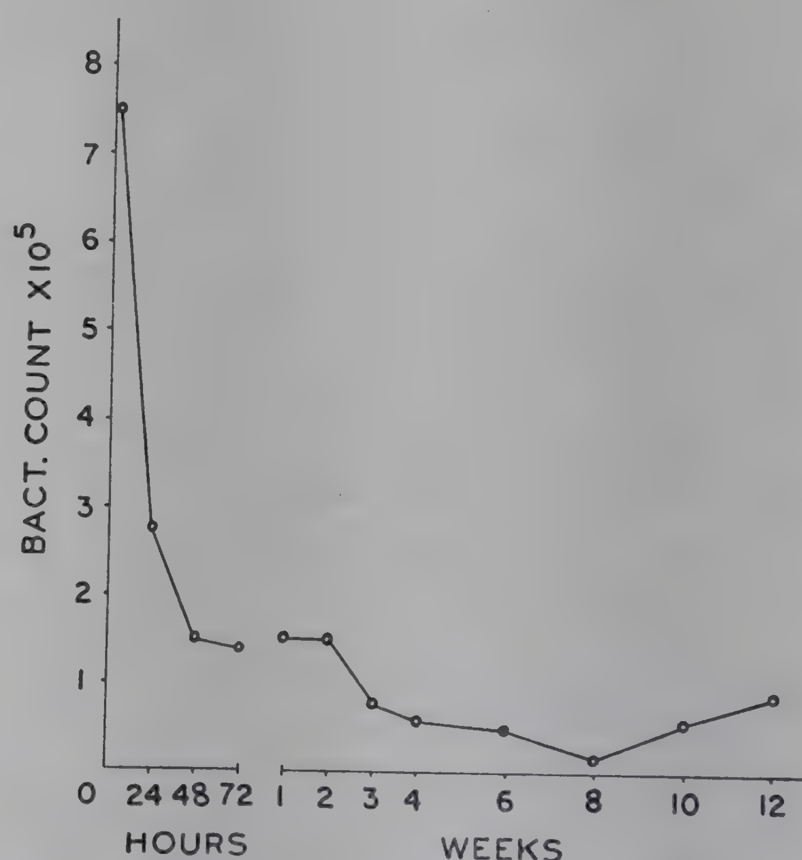

Fig 1. Rate of disappearance of M. Leprae inoculated into mouse foot-pad.

Fragmented A.F.B. and their viability

It is generally believed that the intact and evenly stained "solid forms" of *M. leprae* are viable whereas the unevenly stained "fragmented forms" are dead. This was based on the observations of Rees and Valentine (1962) wherein a parallelism was

discovered between the unevenly stained bacilli under light microscope and the same bacilli under electron microscope. The electron microscope findings definitely indicate cytoplasmic changes. This opinion of non-viability of fragmented bacilli has also been confirmed by Shepard (Mc Rae and Shepard 1971). However, the experiments carried out by Desikan did not confirm that non-solid forms are nonviable (Desikan 1976). In a series of 20 experiments, mouse footpads were inoculated with harvested material from infected mice containing *M. leprae* in different grades of morphology ranging from the highly fragmented coccoid forms to the evenly staining solid bacilli, and including broken bacilli, beaded bacilli and unevenly stained forms in different proportions. In 8 experiments solid bacilli formed 0%, while in 12 experiments, the solid bacilli ranged from 1 to 10%. In both these groups there was multiplication in the mouse footpads. Quantitatively, the yield of bacilli was not significantly different in the two groups. An inoculum containing only coccoid and highly fragmented forms also showed significant multiplication. These findings therefore positively indicate that all the irregularly stained and "non-solid" bacilli are not necessarily dead. It is true that treatment with specific drugs is followed by a fall in the M.I. and it is also possible that dying germs might show changes in their morphology; but one definite fact that the studies of Desikan point out is that an attempt to label a germ as alive or dead by its morphology is highly equivocal and subject to a serious error.

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HUMORAL ANTIBODIES AND IMMUNE COMPLEXES IN LEPROSY[1]

Sergio Estrada-Parra[2] and Oscar Rojas-Espinosa[2]

ABSTRACT

In the past, the search for specific antibodies in patients with leprosy was hampered due to the lack of well defined antigens and appropriate test systems. With the recently developed methodology these difficulties are now partially overcome, but a great deal of studies have to be done in order to understand the precise meaning of the kinds of antibodies frequently found in the sera of lepromatous patients. Anti-mycobacterial antibodies are present in most lepromatous patients and are scarce or absent in the tuberculoid cases. These antibodies do not seem to play an important role in the elimination of the M. leprae but they may be involved in the pathogenesis of the disease as they form immune complexes that promote injury in blood vessels, skin, kidney and other parts of the body.

When a foreign substance or antigen penetrates the body, this substance is recognized by the body's immune system and an immune response is generated. The induced immune response has two varieties : the cell-mediated immune response and the humoral immune response. The humoral immune response depends on the formation of soluble factors called antibodies. The antibodies are glycoprotein molecules which have the property of reacting in a specific manner with the antigen that elicits them. There are 5 classes of antibodies : IgG, IgM, IgA, IgE and IgD, each with particular biological properties. The antibody molecules, in this paper "Y" shaped, have sites that react specifically with the antigen (antigen combining sites), and other portions on which their biological properties depend (Fig. 1).

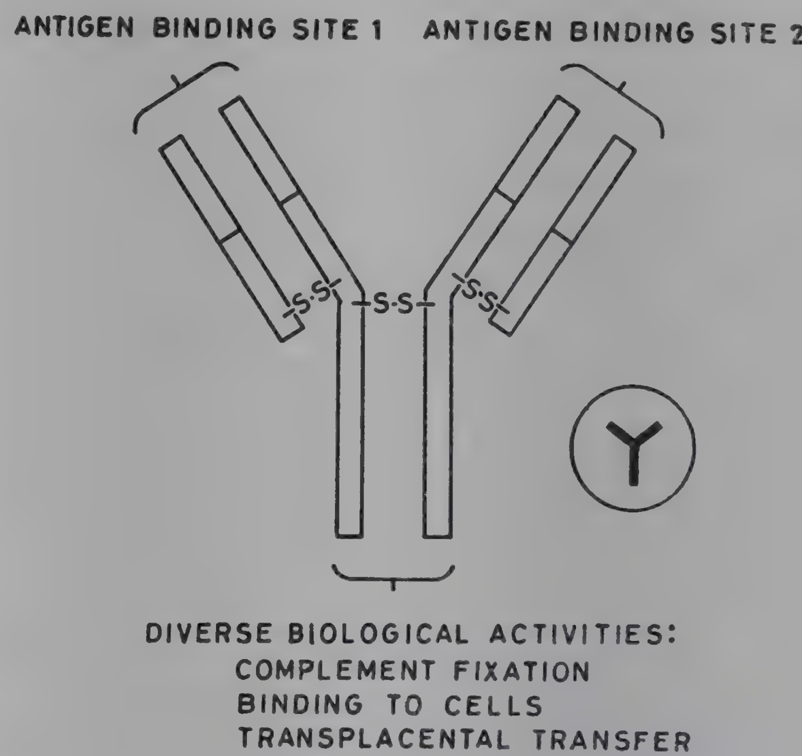


Fig. 1. The basic structure of an antibody molecule consists of four polypeptidic chains held together by disulfide bonds.

In many infectious diseases the antibodies play an important role in the elimination of micro-organisms or their toxic products. In diphtheria and tetanus, for instance, the germs produce potent toxins which can injure normal tissues. If specific antibodies are present, they combine with and neutralize the toxins, avoiding the tissue damage (Fig. 2). In certain viral diseases antibodies also neutralize

1. Personal experiments mentioned here were carried out with the aid of CONACYT, WHO and CDGCYT.

2. Fellows of the COFAA del I.P.N.

virus particles, blocking their access to susceptible cells and, in so doing, preventing the cellular lesion (Fig. 2). In some bacterial diseases antibodies, with the help of Complement*, increase the destruction of the bacteria by enhancing the phagocytosis of leucocytes, or by lysis (Fig. 3). However, in some other bacterial diseases antibodies do not seem to be of any value in the elimination of the germs. This happens, for instance, in tuberculosis, leprosy, and most mycotic diseases.

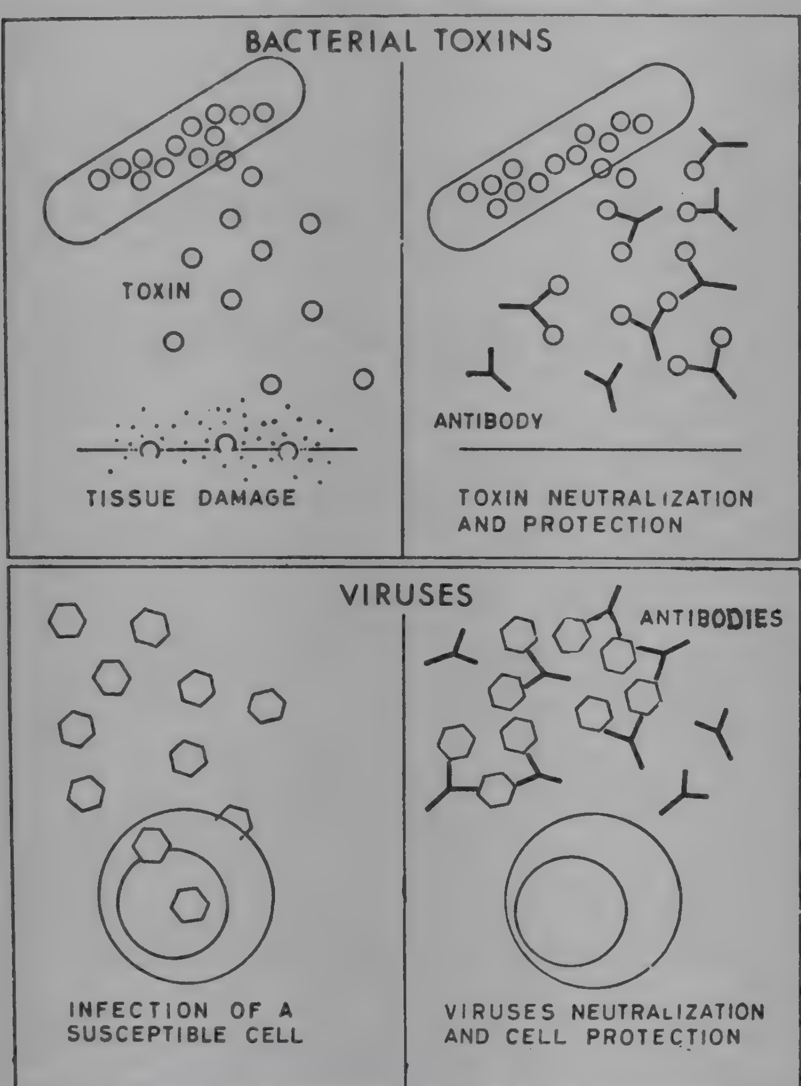


Fig. 2. Antibodies are able to neutralize toxins and virus particles and in this way they confer protection to the host's tissues.

On the other hand, it has been found that antibodies are also capable of eliciting tissue damage. There are four ways by which antibodies can injure the tissues. In the first type, there is the formation of antibodies with strong affinity for certain cells. This is the case of the classic allergy where the antibodies belonging to the class E (IgE) attach themselves on the membrane of mast cells and basophils. Once the antibodies are on the cell membranes and contact the antigen, the antigen-antibody reaction is the signal for the release of substances which promote an increase in the vascular permeability, contract smooth muscles and lead to inflammatory reactions (Fig. 4).

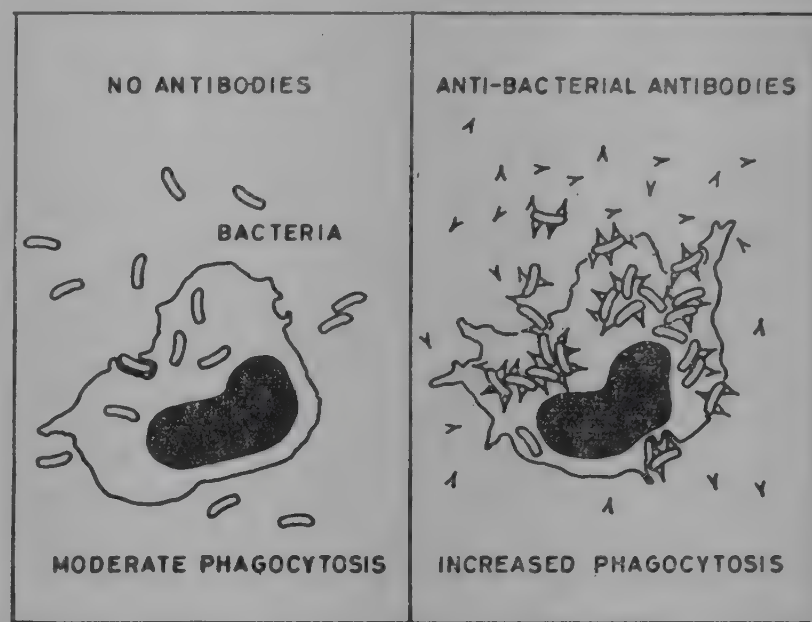


Fig. 3. When microorganisms are coated with specific antibodies, they are more easily ingested and destroyed by phagocytic cells.

In the second type, there is the formation of antibodies against the surface of cells or against substances (such as drugs) that attach themselves to cells. Under these conditions the cell which has bound the antibodies can be destroyed by the action of complement, by enhancing the phagocytic process, or can be killed by the so called "killer cells" (Fig. 4).

The third type depends on the formation of antigen-antibody complexes and there are two prototypes. In one of them, there are large amounts of circulating antibodies and when the antigen appears there is the formation of microprecipitates which fix complement and attract neutrophile leucocytes that release enzymes capable of destroying tissue components (Arthus type, Fig. 5). In the other case, there is a large amount of circulating antigen and when a specific antibody appears soluble immune complexes are formed. These complexes may deposit on the arteriolar endothelia and on the glomerular basement membranes in the kidney. As above mentioned, in some cases there is complement fixation, arrival of neutrophile leucocytes and tissue damage.

* A system of 9 components present in the plasma and other body fluids.

There is another type of antibody-mediated hypersensitivity, the so called "stimulatory" in which antibodies directed against a cell do not destroy but stimulate it to produce substances in abnormally high amounts. This type has been described in a disease called thyrotoxicosis in which antibodies against the thyroid gland enhance the production of thyroid hormones (Fig. 6).

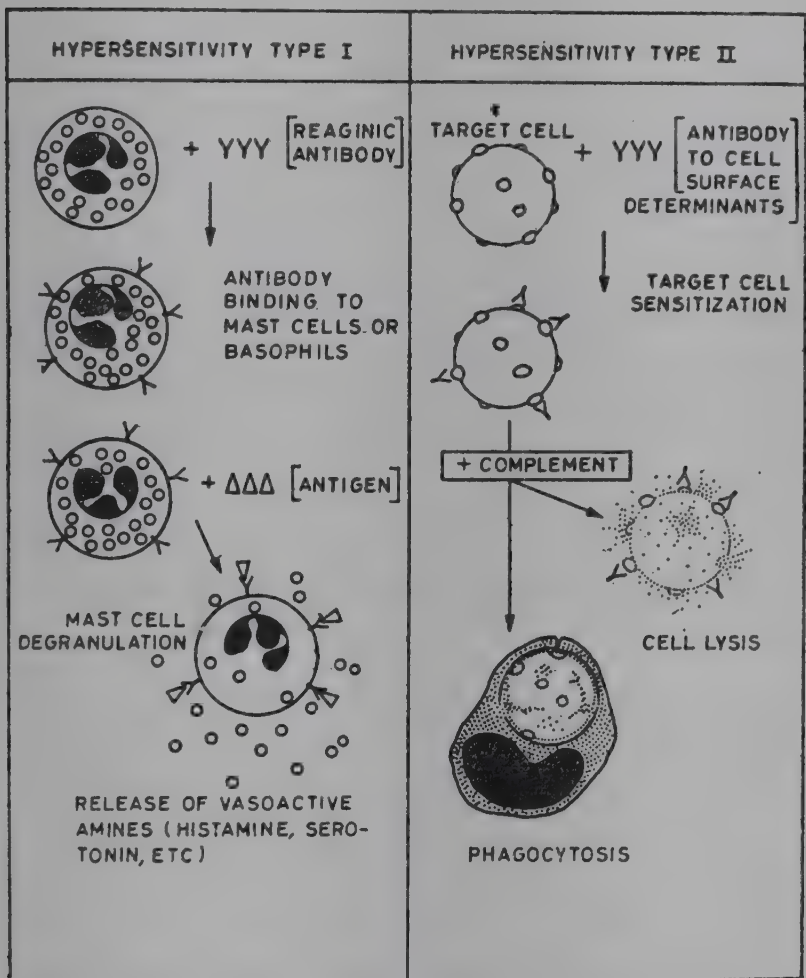


Fig. 4. (a) In the classic allergy (hypersensitivity type I) the reaginic antibodies (IgE) attach themselves to mast cells and basophils and when they make cotact with the antigen, degranulation occurs. In the process vasoactive amines are released which lead to inflammatory changes. (b) In the hypersensitivity type II, the antibody attached to the cells surfaces makes them easily phagocytable or destroyed by complement or by certain killer cells.

Humoral immune response in leprosy.

The humoral immune response in leprosy has been extensively studied in many laboratories all over the world. As many excellent reviews on this subject have been published and are easily available, we would like just to point out the highlights on the area and then we would summarize our own work on it.

It is generally accepted that the ability of patients suffering from any form of leprosy to respond with circulating antibodies to different antigenic stimuli is not depressed but normal, and in certain cases it is increased. This finding is of particular importance in the case of lepromatous leprosy where many aberrations in cell mediated immunity have been described. These aberrations are more apparent in cases of long lasting leprosy.

As lepromatous leprosy is the malignant form of the disease, attention will be focused on this type of leprosy : leprosy patients respond normally to the injection of mycobacterial antigens, typhoid-paratyphoid vaccine, smallpox vaccine, and other stimuli. Many lepromatous patients show a high incidence of auto-antibodies (rheumatoid factor, antinuclear antibody, antithyroglobulin antibody, anti-sperm antibody, and others). Most of the patients develop hypergammaglobulinemia, part of which seems to be non-specific and part of which might account for the auto-antibodies mentioned above.

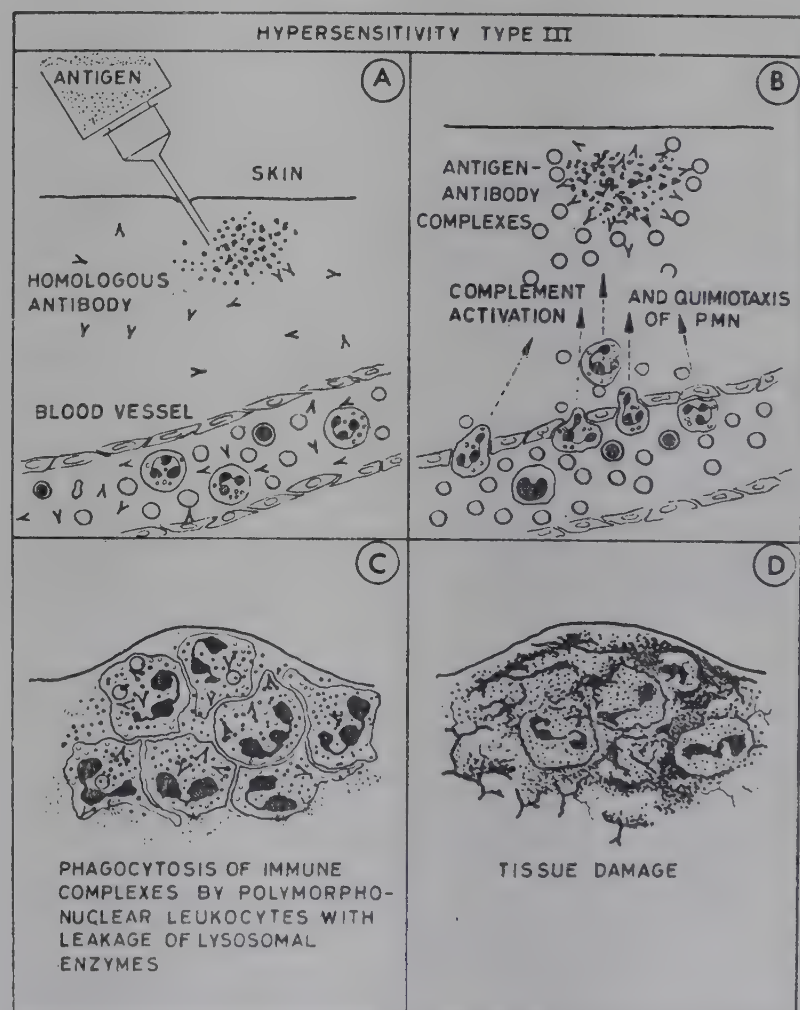


Fig. 5. In the hypersensitivity type III, the antibody combines with its antigen and activates the complement system. In the process, chemotactic factors are released which attract polymorphonuclear leucocytes (PMN) to the site of reaction. Tissue damage is accomplished, among many other things, by hydrolytic enzymes derived from the PMN, by the activated complement system, and by anatomical changes in the site adjacent to the antigen-antibody reaction.

The ability of lepromatous patients to respond normally with antibodies to several thymus-dependent antigens suggest that if they present a depression in their cell mediated immunity, this depression has to be very specific affecting only the lymphocyte subpopulation committed with the recognition of *M. leprae* (lepromatous patients are unable to develop a skin reaction against lepromin but they do so with other antigens). Many questions remain to be answered regarding the relationships between cell-mediated immunity and humoral immunity in patients with lepromatous leprosy. One apparent paradox is the general consent that there exists in these patients a lack of *M. leprae*-reactive T-lymphocytes and the fact that they contain anti-*M. leprae* antibodies in their blood whose titer is in direct relation to the bacterial load (*M. leprae* is a thymus dependent antigen).

STIMULATORY HYPERSENSITIVITY

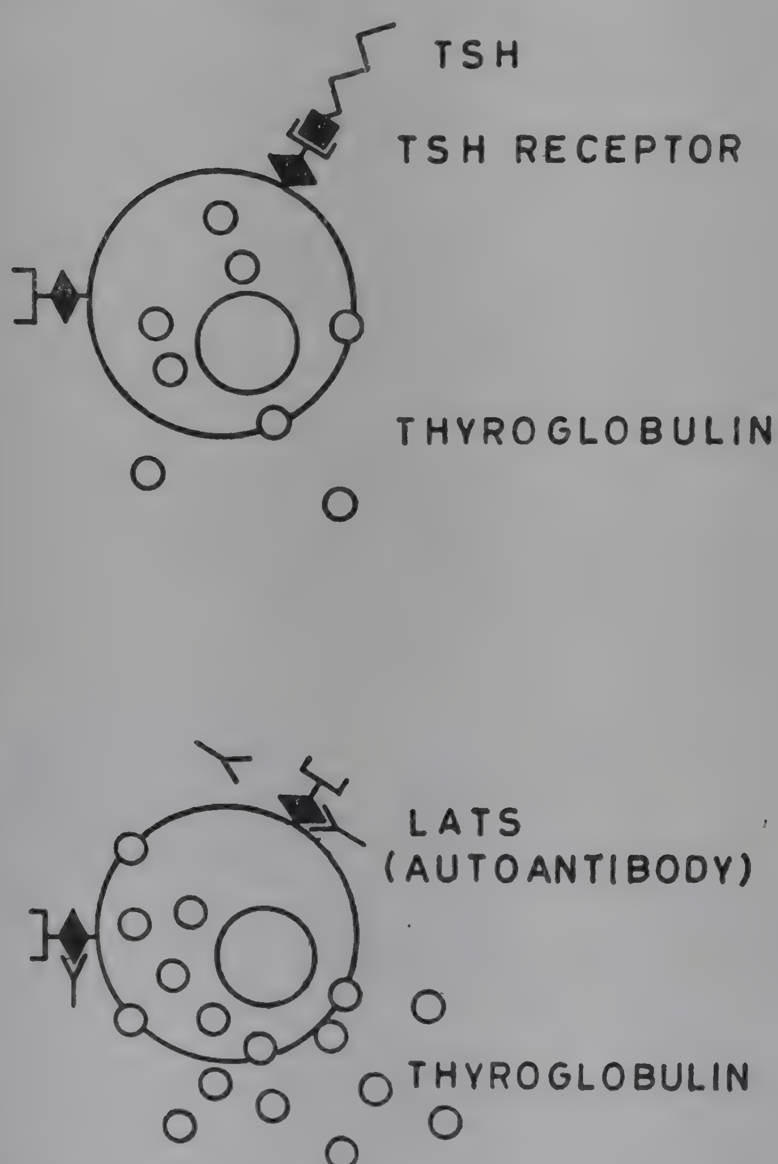


Fig. 6. An example of stimulatory hepersensitivity is found in a disease called thyrotoxicosis. Here, an autoantibody (long acting thyroid stimulator or LATS) combines with an antigen present on the membrane of the thyroid cell in a site close to the thyroid stimulant hormone receptor (TSH) or with the receptor itself and as a result, it stimulates the overproduction of thyroglobulin.

In relation to the levels of complement in leprosy, and talking in a general way, it has been found that in most of the patients the total hemolytic activity of complement is not decreased. A transient decrease in the level of hemolytic complement has been communicated in patients undergoing severe forms of leprosy reaction. This has been explained on the basis of complement consumption triggered by excess of antigen-antibody complexes (see below). On the other hand, when individual complement components have been quantitated, normal or variably elevated levels have been found in most of the cases. The elevated levels in one or two of the studied components have been assumed to be the response of the organism secondary to the complement consumption as an effort to compensate for the loss.

Circulating antimycobacterial antibodies and immune complexes in leprosy.

The study of humoral antibodies to *M. leprae* in patients with leprosy was hampered by the lack of specific antigen preparations to detect them. It is well known that *Mycobacterium leprae* can not be cultured in test tubes like *Mycobacterium tuberculosis* and other related microorganisms. The search for antibodies, and antigens from the leprosy bacillus, was opened when Bojalil and his co-workers isolated an antigenic substance from Nocardia, a microorganism related to *M. leprae*, which cross-reacted with some sera from patients with leprosy. When this material was further purified, it was found to be a polymer of sugars (polysaccharide I) made of D-galactose and D-arabinose. Later on, we isolated from human lepromatous tissue a similar substance which by immunological criteria showed to be identical to the one isolated from Nocardia (Fig. 7). The next step was the purification of *M. leprae* from the lepromatous tissue. When the purified bacillus was broken down by ultrasonic treatment it released, among many other things, a polysaccharide which was again immunologically identical to the ones mentioned above. Therefore, we isolated the first well defined antigen from *M. leprae*.

At the same time we started to work with the germ that causes leprosy in mice and rats, the *M. lepraemurium*. Soon we found that

both microorganisms, *M. leprae* and *M. lepraemurium*, had common antigens and that extracts from purified *M. lepraemurium* could be used to look for antibodies in patients with leprosy (Fig. 8). The antigenic extract prepared from *M. lepraemurium* proved better than the one isolated from Nocardia, because it gave us more positive reactions in the immunological tests.

Fig. 7. 1. Polysaccharide preparation isolated from lepromata. 2. Serum from a patient with active tuberculosis. 3. Polysaccharide I, isolated from *Nocardia brasiliensis* (Poly INb). 4. Serum from a patient with lepromatous leprosy (one extra band is observed). 5. As in No. 2. 6. Serum from a patient with lepromatous leprosy (two extra bands are noted).

Recently we have adapted the counter-immunoelectrophoresis technique to detect antibodies against *M. leprae* by using extracts from B.C.G. (the microorganism used in vaccination against tuberculosis) or *M. lepraemurium*. With this new method we have found that most lepromatous patients have circulating anti-mycobacterial antibodies and that in the tuberculoid patients these antibodies are quite less frequent or even absent (Fig. 9). The finding of specific antibodies has also been achieved by other researchers and in general we all agree that the anti-mycobacterial antibodies, like in other mycobacterial diseases, play a little or no role in the elimination of the leprosy bacillus (probably because of the predominantly intracellular localization of the parasite). On the other hand, we favoured the possibility that anti-mycobacterial antibodies might contribute to the host's tissue damage as they do not seem to protect him. Bearing in mind that lepromatous patients lack specific cell mediated immunity to *M. leprae* antigens, which in fact is one of the ways by which *M. leprae* is eliminated, and that these patients have circulating antibodies and/or antigens, we postulated that immune complexes could be present in the sera of the patients. Our first attempt to demonstrate that was successful using the whole bacillus and fluorescent antibodies against the common polysaccharide. Under these conditions we showed that the leprosy bacillus, in the blood, had antibodies attached to it. However, at that time, the immune complexes made of soluble products from *M. leprae* and antibodies, that could be of great relevance in the pathology of leprosy, were not identified due to the lack of an appropriate method.

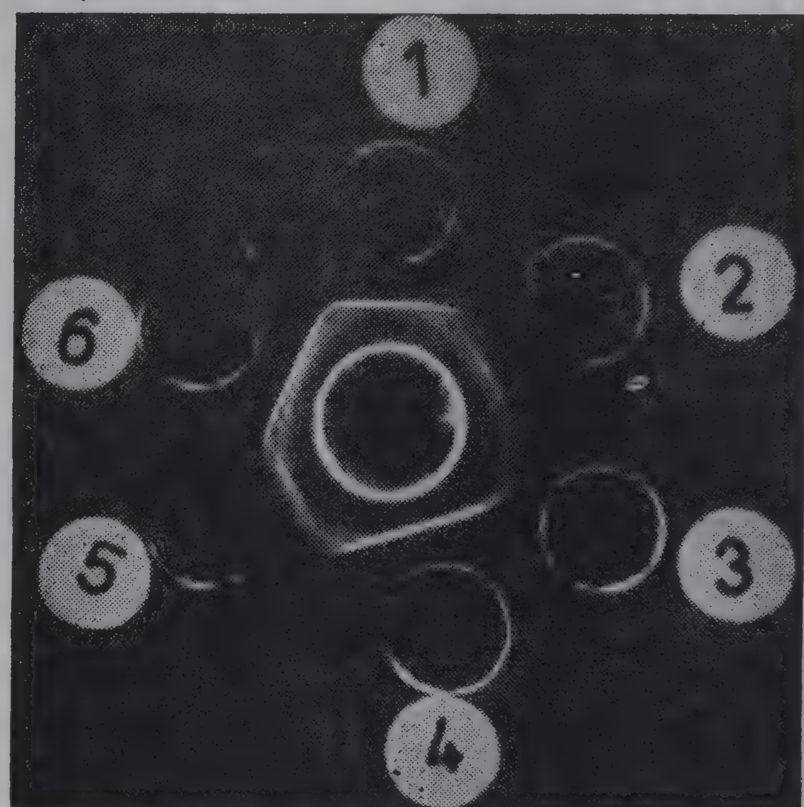


Fig. 8. 1. Polysaccharide I from *N. brasiliensis*. 2. Purified polysaccharides from *M. lepraemurium*. 3. Purified polysaccharide from *M. leprae*. 4. Polysaccharide I from *N. brasiliensis*. 5. Purified polysaccharides from *M. lepraemurium*. 6. Purified polysaccharides from *M. tuberculosis*. Center well : serum from a patient with lepromatous leprosy.

In 1970 Kunkel and his co-workers reported that soluble immune complexes could be detected by the use of the C1q subcomponent of complement. We took advantage of this discovery and found the presence of immune complexes in the sera of leprosy patients. These immune complexes were present in higher proportion in patients with lepromatous leprosy and were almost absent in tuberculoid patients. Furthermore, it was found that in patients with erythema nodosum

leprosum or E.N.L. (a complication of patients with lepromatous leprosy), the incidence of immune complexes was even higher than in lepromatous patients without E.N.L. The immune complexes were also very frequently found in patients with Lucio's reaction (a complication of lepromatous leprosy with necrosis) (Fig. 10).

Once the presence of immune complexes was established by the C1q method, we used still another method to corroborate their presence. The method was described many years ago by a Brazilian doctor, Otto Bier, and it consists in the injection of sera containing immune complexes into the skin of a guinea pig followed by a dye. With this method we found that immune complexes were present in the serum of patients with lepromatous leprosy and in higher proportion in the serum of patients with E.N.L. and Lucio's reaction. Since the presence of immune complexes was unequivocally demonstrated, an experiment was designed to elucidate their composition (Fig. 11). The sera from patients with immune complexes were pooled and precipitated with a salt solution (ammonium sulfate), then the precipitate was washed, dissolved in saline, and treated with a glycine buffer at low pH (this procedure brings apart the components of the immune complexes). The antibodies' moiety was then precipitated with 50% ammonium sulfate and the supernatant, containing the antigens, was decanted. The sediment containing the antibodies was dissolved in saline and both solutions of antigens and antibodies were extensively dialyzed. The separated antibodies reacted with an extract of *M. lepraemurium* and, the antigens with sera from lepromatous patients.

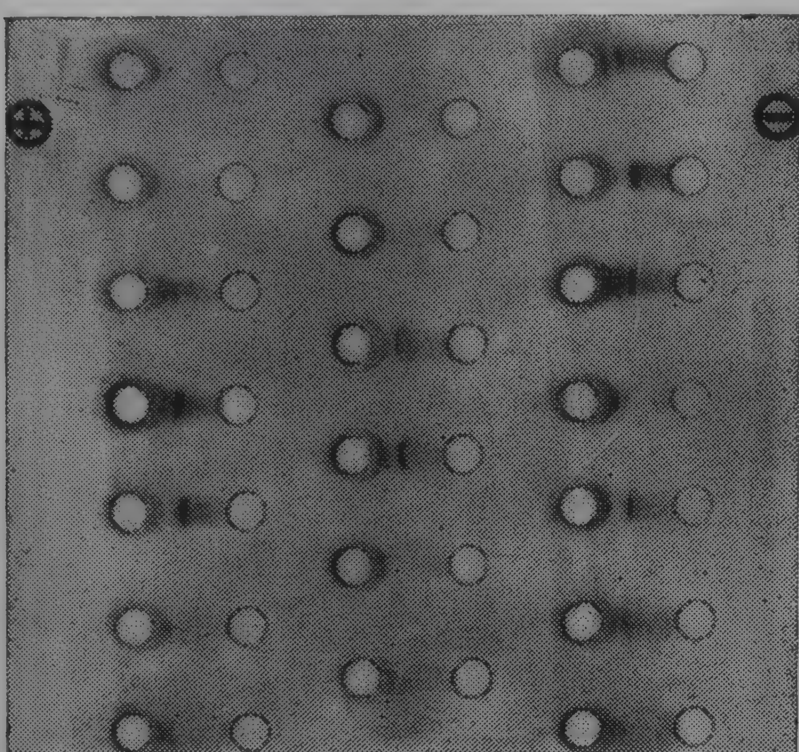
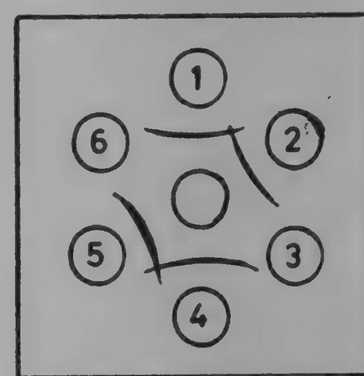


Fig. 9. The counterimmunoelectrophoresis (CIE) technique is a simple, rapid and reliable tool for the demonstration of antimycobacterial antibodies in the serum of patients with lepromatous leprosy. In the picture, the wells in the left vertical row of each pair held the leprosy sera, while the holes in the right vertical rows contained an aqueous extract prepared from purified *M. lepraemurium* as the antigen.



1. HEAT-AGGREGATED GAMMA-GLOBULIN
2. & 5. LEPROSY SERA WITH SOLUBLE IMMUNE COMPLEXES
3. NORMAL HUMAN SERUM
4. SERUM FROM A PATIENT WITH S.L.E. HAVING IMMUNE COMPLEXES
6. PHYSIOLOGICAL SALINE SOLUTION

CENTER WELL: PURIFIED C1q

Fig. 10. When soluble immune complexes are present in leprosy sera at an adequate concentration, they can be demonstrated by their reaction with the C1q subcomponent of complement. This subcomponent C1q also reacts with heat-aggregated gammaglobulin forming a band of precipitation.

When the antigens' solution was reduced to a small volume and then hydrolyzed with acid, the presence of arabinose as a component of *M. leprae* was demonstrated by paper chromatography. Therefore, at least some of the immune complexes in leprosy sera are made of antibodies against *M. leprae* and soluble antigens from the microorganism. These immune complexes, may play a role in the injury (type III) frequently found in lepromatous patients.

It is well known that the lepromatous type of leprosy is the malignant form of the disease. At the present time we are sure that

patients with this type of leprosy have circulating antibodies and that they do not protect them. Morever these patients have a large load of *M. leprae* part of which release soluble components as a result of degenerative and destructive processes. The released antigenic components react with specific antibodies forming complexes which circulate in a soluble form.

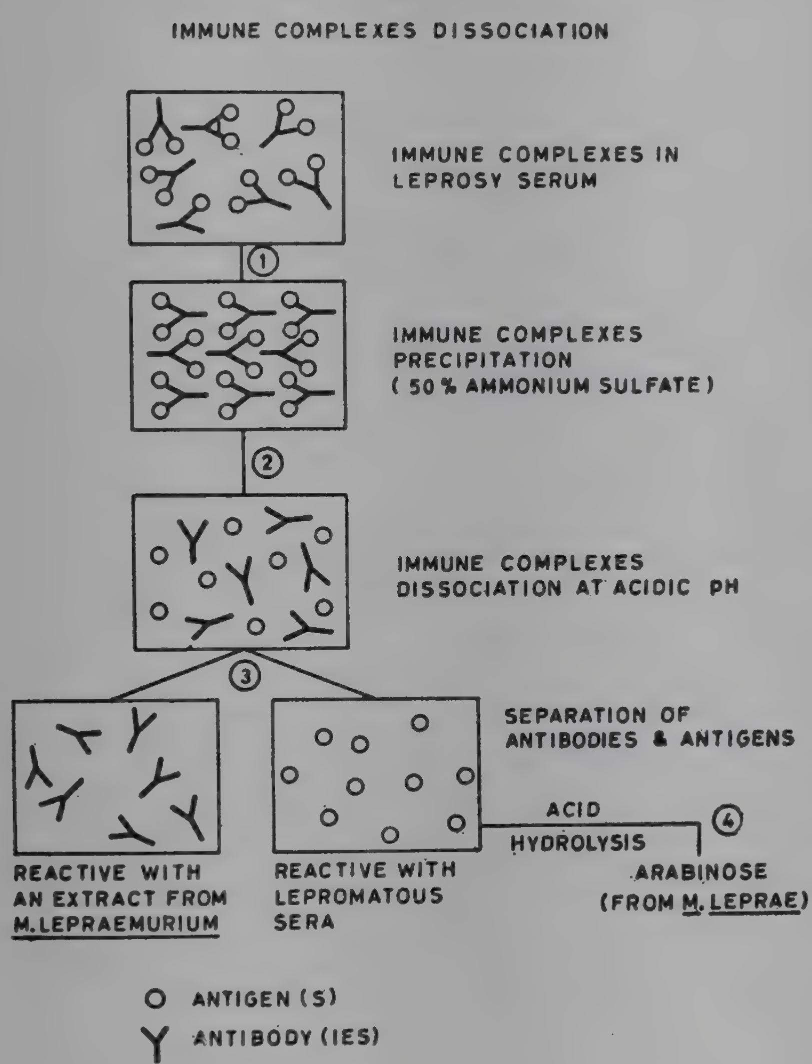


Fig. 11. Part of the soluble immune complexes present in the sera of patients with lepromatous leprosy are made of mycobacterial antigens (*M. leprae*) and anti-mycobacterial antibodies. They can be dossociated and studied as shown in the diagram.

Lepromatous leprosy is a very interesting disease in which the lack of a specific cell mediated immunity associated with a high level of circulating anti-mycobacterial (and other) antibodies, leads to the formation of soluble immune complexes which in turn may be important mediators of tissue damage.

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IMMUNOLOGICAL BASIS OF REACTIONS IN LEPROSY

M. F. R. WATERS

Although it was held for many years that leprosy reactions must have an immunological basis, it is only in the last decade that evidence has been produced in the two major groups of reactions to confirm this hypothesis.

1. Erythema Nodosum Leprosum (Lepromatous Lepra Reaction)

Erythema Nodosum Leprosum (ENL) occurs in patients at or near the lepromatous end of the leprosy spectrum, where cell-mediated immunity (CMI) against *Mycobacterium leprae* is very low or absent. Such patients harbour large numbers of leprosy bacilli, which are present in those tissues in which ENL lesions develop, in particular skin, nerve, the anterior part of the eye, testis and lymph node. In the small number of borderline-lepromatous (BL) patients who suffer from ENL, the skin papules always appear at sites containing *Myco. leprae,* and especially in succulent plaques, the BL lesions with the highest bacterial load. Therefore, in most systems of the body, ENL lesions are associated with the presence of leprosy bacilli.

Furthermore, the ENL lesions are associated with *dead* leprosy bacilli. The reaction is far more common in treated than in untreated patients, the first attack frequently, occurring between six and 12 months after commencing treatment with dapsone, or between two and six months after commencing rifampicin; that is, at the very time when the great majority of the leprosy bacilli have been killed, and when the patient has his heaviest load of dead *Myco. leprae*. Even in untreated leprosy, as Fernandez showed in 1936, well before the introduction of sulphone therapy, ENL lesions contain fragmented (dead) leprosy bacilli.

Patients with lepromatous leprosy also have high titres of circulating antimycobacterial antibodies. High levels of IgG immunoglobulin are consistently found in the sera of untreated lepromatous patients; high levels of IgA and IgM have also been described, but appear more variable.

Histologically, on a background of treated or quiescent lepromatous leprosy, there is an intense perivascular polymorpho-nuclear leucocytic infiltration, and significant, often severe, vasculitis may be detected. These findings are reminiscent of that seen in the Arthus reaction in experimental animals. The Arthus reaction is an allergic reaction which occurs when there is a very high concentration of conventional antibody such as IgG in the circulation, and a high concentration of soluble antigen lying extravascularly in the tissue spaces. The reaction may be obtained by injecting an experimental animal (such as a rabbit or guineapig) with an antigen to which it has previously been sensitised. The reaction occurs primarily in the wall of small blood vessels as a result of antibody from the circulation meeting antigen diffusing inwards from the extravascular space; antigen-antibody complexes can be demonstrated in the vessel wall. These immune complexes fix and activate complement—the complicated enzyme system present in fresh serum which is involved, for example, in the lysis of red blood corpuscles by antibody—which in turn attracts the polymorphonuclear leucocytes. Eventually the vessel wall becomes damaged. Arthus sensitivity has been detected in man in a number of not very common pulmonary diseases, for example pulmonary aspergillosis and "Farmer's lung". When the appropriate fungal antigen is given intradermally, the patient develops a red oedematous lesion at the injection site, which reaches its peak in four to 12 hours, and where immune complexes and complement may be detected in the dermal blood vessels.

When Turk and his colleagues studied biopsies of ENL lesions in 38 lepromatous patients, immunoglobulin (IgG) and complement (the component βIC/βIA was the one studied)

were detected in areas of polymorph infiltration in 20 patients. No such deposits were found in lepromatous skin lesions from 13 patients who did not have ENL. The deposits seen were granular in form, and did not correspond to the areas of bacterial infiltration. Deposits were sometimes demonstrated within the walls of blood vessels in the deep dermis. Although techniques were not (and are still not yet) available for studying specific *Myco. leprae* antigen in tissues, Turk's group were able to obtain evidence that non-specific mycobacterial antigen was present in the deposit containing immunoglobulin and complement in seven of the ENL lesions. However, groups or globi of *Myco. leprae* failed to stain with the appropriate reagent. Therefore they suggested that the antigen moiety of the immune complex might be a soluble, cytoplasmic (not surface) mycobacterial antigen released from dead leprosy bacilli.

Over the last six to eight years, since this work was published immunological methods for studying immune complexes have been considerably developed and refined. There is urgent need for these newer methods to be applied to ENL to confirm and extend Turk's studies. Nevertheless, the latter provide good evidence that ENL skin lesions are comparable to the Arthus phenomenon; that is, that they are due to the local formation of immune complexes. A similar mechanism is assumed to be responsible for the development of ENL lesions in those other tissues which also contain numerous *Myco. leprae,* that is for ENL neuritis, lymphadenitis, orchitis and iridocyclitis. Even in ENL arthritis, fragmented (dead) leprosy bacilli and degenerating polymorphs have been found in the synovial exudate. But in addition, systemic upset with fever commonly occurs in episodes of ENL, significant proteinuria may be detected, and both Drutz and Guttman, and Bullock and his colleagues have produced evidence of immune complex deposition in the kidney. These observations suggest that, as well as Arthus-like reactions locally, patients with ENL may develop illness due to circulating immune complexes. To date, this aspect has been little studied, and much further work is indicated. However, it has long been known that cryoglobulins may occur in lepromatous sera. More recently, using the relatively non-specific Clq technique, groups in Mexico, California and London all found evidence for the presence of immune complexes in the serum of patients suffering from lepromatous leprosy; furthermore, the two latter groups reported that immune complexes were more frequently found in sera from patients suffering from ENL than in sera from lepromatous patients not in reaction.

To date, no animal model of ENL has been discovered.

2. Reversal (Upgrading) Reactions

These reactions occur in borderline-tuberculoid (BT), borderline (BB), borderline-lepromatous (BL) and very occasionally in subpolar lepromatous (LLs) leprosy, most developing within the first year of therapy. The skin lesions become red and swollen, some patients become mildly febrile and there is frequently severe peripheral nerve involvement. The lesions usually remain in reaction for several months.

It has been shown that the position of the individual patient on the leprosy spectrum is related to his ability to develop specific cell-mediated immunity (CMI) against the leprosy bacillus. During a reversal reaction many patients change in classification, moving across the clinical spectrum towards tuberculoid. Histologically, in addition to oedema and some hyperaemia, the skin granuloma corresponds to the type of leprosy the patient has or is developing. Associated with the switch towards tuberculoid, there is usually an early influx of lymphocytes. The cytology of the host cells (cells which may contain *Myco. leprae*) becomes less histiocytic and more epithelioid. The number of bacilli in the granuloma progressively diminishes. These changes suggest that the patient is regaining CMI as the bacterial load is being reduced by therapy.

This concept is supported in many different ways. In those patients who move across the spectrum as far as BB/BT or to BT, the lepromin test becomes positive or more strongly positive. Changes monitored histologically in lymph node biopsies are also compatible with increased CMI. In lepromatous leprosy, the paracortical areas of lymph nodes are replaced by macrophages full of bacilli and are depleted of lymphocytes, presumably T-cells, while B-cell areas often show increased activity; in reversal reactions lymphocytes can be seen to begin to appear in the paracortical areas around the postcapillary venules, suggesting a return of T-cell activity.

Godal and his colleagues have studied the specific lymphocyte transformation test (LTT)

response during reversal reactions. In this test, lymphocytes from the peripheral blood of the patient are stimulated by whole *Myco. leprae;* in LL and BL leprosy no, or virtually no, lymphocytes are transformed, whereas good transformation is obtained in BT and very good in TT leprosy (averaging around 6% of lymphocytes in the former and 22% in the latter). During reversal reactions the LTT response increases, and this has been interpreted as proof of increase in CMI. However, it is probable that the specific LTT does not correlate directly with cellular immunity (i.e. with the ability of the host to eliminate *Myco. leprae*), but rather with the strength of the delayed hypersensitivity (allergic) reaction shown by the patient. Thus LTT tests may frequently be stronger in actively inflamed BT (in reversal reaction) than in TT, although the response decreases usually to around average BT levels when the reaction settles. Moreover, the response in the LTT may vary depending on the nature of the antigenic preparation used to stimulate the lymphocytes. Thus in BB and BT patients in reversal reaction, those whose reaction principally involves nerve (that is, those suffering from active neuritis and nerve damage) may show a stronger LTT response to sonicated *Myco. leprae* used as antigen than to whole bacilli, whereas the opposite is found in those patients whose reversal reaction principally involves skin lesions.

Reversal reactions have been obtained experimentally in two different ways. Both Bullock and Jacobson and their colleagues found that a small proportion of lepromatous patients administered transfer factor obtained from the lymphocytes of donors with strong positive lepromin tests subsequently developed mild, short-lived reversal reactions. Rees and Weddell have reported an excellent animal model. They infected thymectomized irradiated inbred (CBA-strain) mice with *Myco. leprae*. Once the mice had developed lepromatous leprosy, they were given syngeneic lymphoid tissue replacement. The mice susbsequently developed reversal reactions, involving especially their ears and foot pads; histologically there was evidence of increased lymphocytic infiltration of the infected tissues with degeneration of bacilli both in skin and in Schwann cells of the peripheral nerves, and the mice moved across the leprosy spectrum from LL to BT.

In conclusion, there is abundant clinical and experimental evidence that reversal reactions are associated with increased CMI, attempted or achieved. However, the individual clinical signs may more closely correlate with increase in delayed hypersensitivity rather than in immunity.

3. Downgrading Reactions

These reactions, which are usually mild, occur in untreated BT, BB and BL patients. They are associated with loss of CMI and a switch across the leprosy spectrum towards lepromatous.

Almost no studies have been carried out on downgrading reactions; indeed, it is usually unethical to perform serial studies as these patients should be started as soon as possible on effective antileprosy treatment.

Furthermore, it appears difficult to postulate an immunological mechanism as the cause of inflammation as the patients are known to be losing immunity. Therefore Bhojwani (personal communication) believes that the majority of downgrading reactions are related to the rapid spread and multiplication of *Myco. leprae*—in other words, the bacteria are in the log phase of multiplication at the time of loss of CMI, and themselves cause the inflammation in the newly-appearing and/or enlarging skin lesions. This could well explain the mild inflammation seen in the majority of downgrading reactions in BB and BL leprosy, although it begs the question why such patients are losing CMI. Perhaps some intercurrent infection or stress has caused non-specific depression of CMI, allowing sufficient multiplication of *Myco. leprae* so that the increased bacterial load in turn produces immunological tolerance. Further studies are indicated.

Nevertheless, as reported in the chapter "Reactions in Leprosy", Pearson and Waters have observed at least one BB/BL patient who developed markedly inflamed skin lesions. He was changed from oral to parenteral thiambutosine (to investigate *prima facie* thaimbutosine resistance); over the course of four months his reaction settled, but he subsequently developed new lesions which clinically and histologically were graded LLs. When his treatment was changed from thiambutosine to dapsone, he soon developed a "reversal reaction" which clinically closely resembled his previous downgrading reaction. It is possible that the latter represented a phase of increased lymphocyte activity prior to

the development of "immunological exhaustion".

Samuel and her colleagues in Ethiopia studied previously untreated BT patients who presented in reaction. They found that the LTT was increased (as in reversal reactions) and therefore postulated that there was no such thing as a downgrading reaction. However, this too avoids the issue, as the great majority of such early BT patients, although untreated, are not in process of losing CMI. Indeed a number of workers believe that in TT and the majority of BT patients, the first appearance of clinical lesions is not due to loss of CMI and the spread of *Myco. leprae*, but rather to the delayed immunological recognition of small numbers of leprosy bacilli, whose local spread and multiplication occurred before the onset of clinical disease. Although the arguments in its favour have still to be formally listed, this concept of the nature of polar and near polar tuberculoid leprosy explains many of the anomalies found in chemoprophylaxis and BCG studies.

4. The Lucio Phenomenon

This reaction has only been observed in the Americas, most of the patients originating from Mexico. It occurs exclusively in pure diffuse, almost certainly polar, lepromatous (LLp) leprosy, the majority of patients being untreated. Clinically it is characterized by crops of painful skin lesions, which resemble irregular, stellate infarctions. Histologically, there is severe vasculitis of the dermal vessels. Quismorio and his colleagues have recently reported the presence of IgG and IgM immunoglobulins and the C3 component of complement in the walls of involved blood vessels. Therefore the Lucio phenomenon may, like ENL, be due to the local formation of immune complexes, but much further work remains to be done.

CELLULAR IMMUNOLOGICAL METHODS IN LEPROSY. THEIR USE IN PROGNOSIS.

JACINTO CONVIT AND MAURICIO GOIHMAN-YAHR,

Leprosy is a disease where the human host and the causative organism develop a prolonged and intimate relationship. The natural unhampered evolution of the disease is protracted, and while the end result may be disastrous, there exists in many cases a healing tendency which may even conduce to actual clinical cure. Available drugs act slowly, and in all cases the host's defense mechanisms are of paramount importance. Antibodies that react with *Mycobacterium leprae* are present in the serum of patients with the disease ; but because they exist even in forms of leprosy that are rich in bacilli and have poor prognosis, their protective role is doubtful. On the other hand, there is evidence that mechanisms of cellular immunity are more directly involved in defense against *M. leprae*. Their existence and integrity determine prognosis.

The immune system and the nature of the immune response have been explained in other chapters. We will just briefly mention that the immune system is concerned with the specific response against antigens. It is formed, as shown in Figure 1 by the "T" and "B" systems. Cellular immunity is under the aegis of the "T" system, which as illustrated in figure 2, is formed by lymphoid cells ("T" cells) which in some stage of their development home and mature in the thymus (hence the "T"). Macrophages are thought to be under the influence of T lymphoid cells.

The functions of T cells may be explored by means of *in-vivo* or *in-vitro* tests. Among the former, intradermal tests and patch tests are the most commonly used. Among the latter, mitogenesis and macrophage migration inhibition are in widest usage. As depicted in figure 3, mitogenesis may be measured by the amount of tritiated thymidine incorporated into the newly formed DNA of lymphoid cells in the presence of specific antigen. Antigens will also stimulate sensitized "T" cells to produce lymphokines. One of these, macrophage inhibition factor (MIF), will inhibit migration of macrophages. This forms the basis of the macrophage migration inhibition test as shown in figure 4.

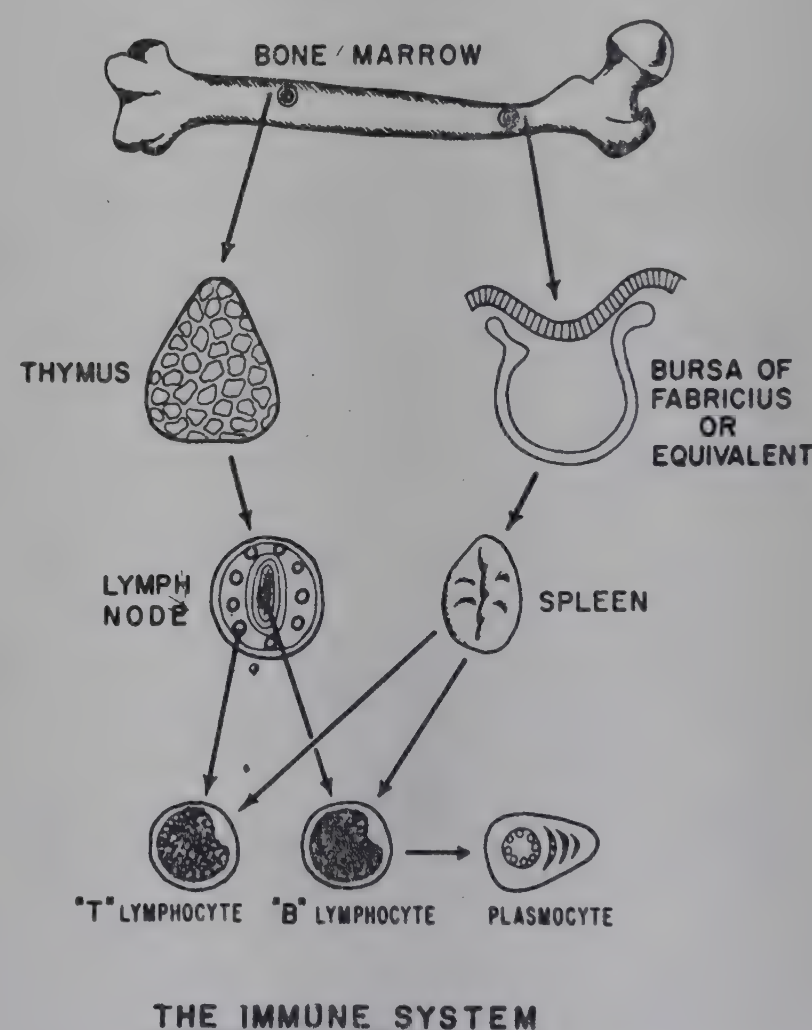

Figure 1. The Immune System. T and B divisions are shown here to be independent. In reality there is a great deal of interrelationship and cross control.

Send Correspondence to : Dr. Jacinto Convit, Instituo Nacional de Dermatologia, Apartado de Correos 4043, Caracas 101, Venezuela.

Correlations between immunologic and clinico-pathologic status of patients with leprosy :

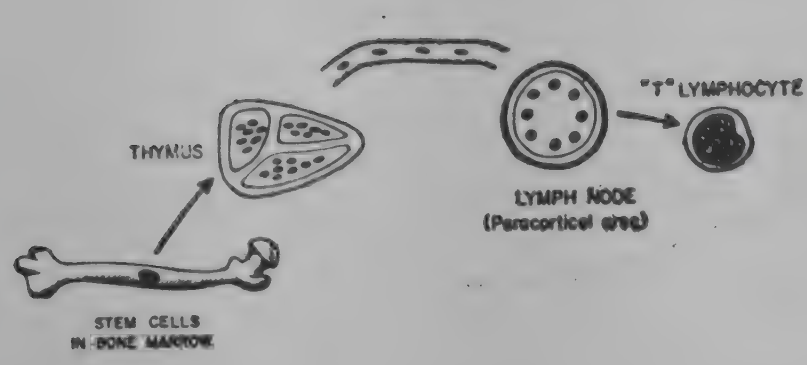

Figure 2. The T system. Note origin of T cells from the bone marrow and their final location in the lymph nodes or in circulating blood.

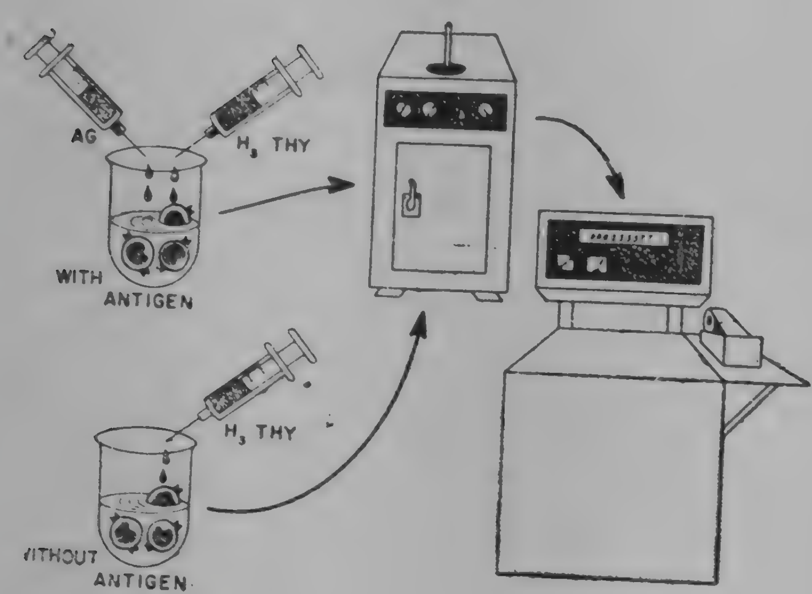

Figure 3. DNA synthesis in the presence and absence of a specific antigen may be estimated by the amount of incorporation of tritiated thymidine into the nucleus of cultured lymphocytes. A scintillation counter is employed.

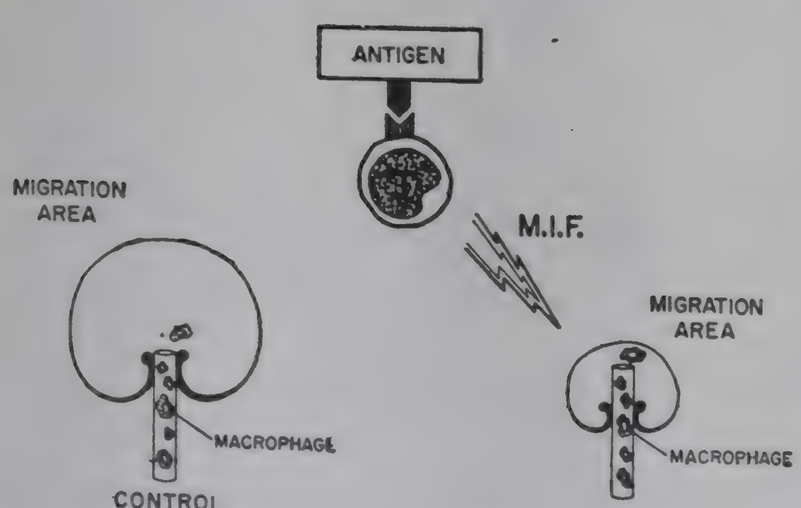

Figure 4. Macrophages inside a capillary tube will migrate out of it. Area of migration may be calculated. MIF will hamper this migration and the area will be correspondingly smaller.

All current classifications admit that in leprosy there are "polar" types (lepromatous and tuberculoid) and intermediate groups as well as a beginning or "indeterminate" form. (See figure 5). It is known also that lepromatous patients have a worse prognosis and respond less well to therapy than tuberculoid ones. Long ago it was found that lepromatous patients were not able to form a nodule of more than 3 mm in diameter thirty days after the intradermal injection of lepromin. (Lepromin is an autoclaved tissue suspension obtained from lepromata. It contained initially 160×10^6 bacilli per ml. Currently 40×10^6 bacilli per ml are used). Tuberculoid patients were able to form such nodule and it had a tuberculoid structure. This is the Mitsuda test. In the Madrid classification (8) the relationship between prognosis, clinical features, basic histology and the results of the Mitsuda test was established. Briefly, lepromatous lesions are granulomas formed by foamy histiocytes with no lymphocytes. Leprosy bacilli are abundant inside histiocytes and the Mitsuda test is negative. This type has a bad prognosis. Tuberculoid lesions are also granulomas, but formed by epithelioid and giant cells as well as lymphocytes. Bacilli are very scarce, the Mitsuda test is positive and the overall prognosis is good. (See figure 6).

Figure 5. Clinical spectrum in leprosy. On the left side we can see lepromatous leprosy, on the right side the tuberculoid pole, upper center borderline lepromatous and lower center borderline tuberculoid leprosy.

It was shown later that tuberculoid granuloma formation after the injection of suspensions of leprosy bacilli could be due to cellular immunologic mechanisms (4). Thus, the presence or absence of a Mitsuda reaction in a

person with leprosy or in "contacts" could be interpreted respectively to mean existence or non-existence of cellular immunity towards *M. leprae*. It became clear, however, that the bacillus itself when injected into a normal person could induce sensitization. Thus, a positive Mitsuda test does not necessarily indicate previous contact with and sensitization against *M. leprae*, but only the capacity to develop cellular immunity against it.

Figure 6. Comparison between clinical and histopathological aspects of leprosy. Left side, lepromatous leprosy with the corresponding structure, a very vacuolized macrophagic granuloma. In the center, borderline lepromatous leprosy with its structure characterized by a macrophagic granuloma with areas where there is moderate epithelioid infiltration and some lymphoid cells. Right side, epithelioid nodules with abundant lymphoid infiltration, corresponding to the clinical picture of tuberculoid leprosy. Hematoxylin-eosin, 40X.

There are not yet available soluble preparations that would be used in leprosy as tuberculin is employed in tuberculosis, that is, to detect previous contact with the causative organism. Instead, the Fernandez reaction, which is the inflammatory response detected 48 hours after the injection of lepromin (1) or else the use of the remainder after particulate matter has been removed from lepromin, have been employed with interesting results to detect previous sensitization towards *M. leprae*.

If we admit that lepromatous patients have a deficit in their cellular immune response towards *M. leprae*, this may owe either to a widespread immune deficiency including also other antigens, or to a circumscribed specific one, only against *M. leprae*. There are examples of the former instance in diseases such as sarcoidosis or Hodgkin's disease. In these, patients may show a partial or total inability to develop cellular immunology against common antigens. Studies were done in which the ability of lepromatous patients to display cellular immunity to contact haptens (e.g. dinitrochlorobenzene), to demonstrate delayed hypersensitivity to the injection of antigens such as tuberculin and oidiomycin (from *Candida albicans*), or the ability of their lymphocytes to enter in mitosis when stimulated with PHA or with specific antigens were studied. The relative proportions of T and B lymphocytes was also estimated. There are conflicting data from many sources. We may summarize the results by saying that there are reports that indicate no evidence of widespread immune defficiency in patients with lepromatous leprosy (6). That the overall response of lepromatous patients to other infections and the incidence of malignant tumours in them does not differ significantly from that of controls. This is so if truly matched controls are chosen and if the non-specific effect of a long standing infection is taken into consideration. Finally, while the response to *M. leprae* as estimated by the Mitsuda test differs strikingly in patients with lepromatous leprosy from that of patients with tuberculoid leprosy, the differences in overall cullular immunity to an array of antigens and tests between lepromatous patients and those with tuberculoid leprosy or normal individuals is more a matter of degree.

From a scientific point of view the Mitsuda test is not a "clean" one. Lepromin is ill defined. The inflammatory response which it induces is not due only to specific immune mechanisms, but also to non-specific factors that influence the final magnitude of inflammmation. Furthermore, quantitation of the latter is at best, rather coarse.

In vitro tests have been applied in leprosy. These include mitogenic response to antigens of *M. leprae* and from other mycobacteria, as well as the ability of lymphocytes to produce lymphokines (mainly marcrophage migration inhibition factor (MIF) when stimulated with such antigens.

Results may be summarized as follows : Lymphocytes from patients with tuberculoid leprosy incubated with suspensions of *M. leprae* or fractions therefrom are able to take a "primitive" appearance and enter in mitosis. Thus they show a characteristic morphology when stained with acridine orange and incorporate tritiated thymidine in the newly synthesized DNA. These lymphocytes also produce lymphokines (in particular MIF)

which may be detected by the use of macrophages from peritoneal exudates of normal guinea pigs. While lymphocytes from lepromatous patients are able to do essentially the same with other antigens, such as those from *Mycobacterium tuberculoisis*, they are unable to react when *M. leprae* suspensions are employed. Lymphocytes from patients of other groups of leprosy respond in an intermediate fashion between these two extremes. (See figure 7). These results confirm and refine the findings already obtained by means of the Mitsuda intradermal test.

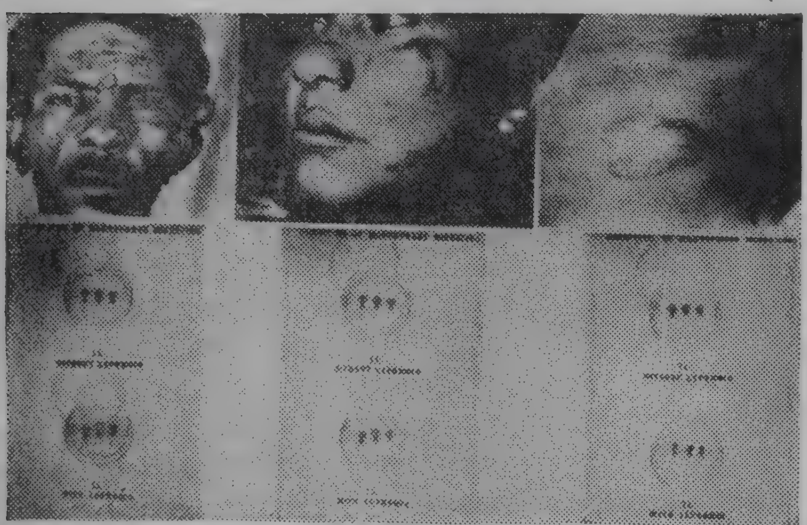

Figure 7. Macrophage migration inhibition test in the different forms of leprosy. Left side, lepromatous leprosy, center, borderline leprosy, both these forms show no inhibition of migration with specific leprosy antigen, right side, tuberculoid leprosy, strong inhibition of migration with the same antigen.

Two points still remained to be clarified, namely, whether macrophages from DERMAL exudates are able to respond to lymphokines (macrophages from the lungs do not) and most importantly, whether there is indeed direct correlation between the lack of response in terms of cellular immunity and diminished digestive capacity of macrophages towards *M. leprae*. The latter is not a purely academic question because there are instances where lack of hypersensitivity to tuberculin is not accompanied by decreased resistance to tuberculosis. Furthermore, experiments that have tried to measure the digestive capacity in vitro of macrophages from lepromatous patients towards *M. leprae* as compared with macrophages from tuberculoid patients and normal individuals, have not given unequivocal results.

The first point has been answered recently by showing in guinea pigs that macrophages from dermal exudates (harvested by means of a chamber implanted at the dermal subcutaneous junction) do not migrate when cultured in vitro with the specific antigen to which donor animals were previously sensitized (5).

The second point has answers in the so called "CCB test" (2). When suspensions of *M. leprae* are injected intradermally into lepromatous patients, the bacilli do not disappear but persist for a long time. Opposite results are seen in tuberculoid patients or normal Mitsuda-positive individuals who will dispose of the injected bacilli and form a tuberculoid granuloma. (See figures 8 and 9). Interestingly, lepromatous patients behave as tuberculoid or normal individuals when other mycobacteria are injected (e.g. B.C.G. or *M. lepraemurium*). Furthermore, if *M. leprae* and another mycobacterium are injected together into the skin of lepromatous individuals, the latter are able to develop a tuberculoid granuloma and to dispose of the injected mycobacteria, including *M. leprae.* The preceding results not only show the specificity of the digestive defect in lepromatous leprosy, but also suggest, although they do not prove, that the primary defect may lie in the lymphocyte. The lepromatous macrophage would need only to be triggered to be able to successfully digest *M. leprae*.

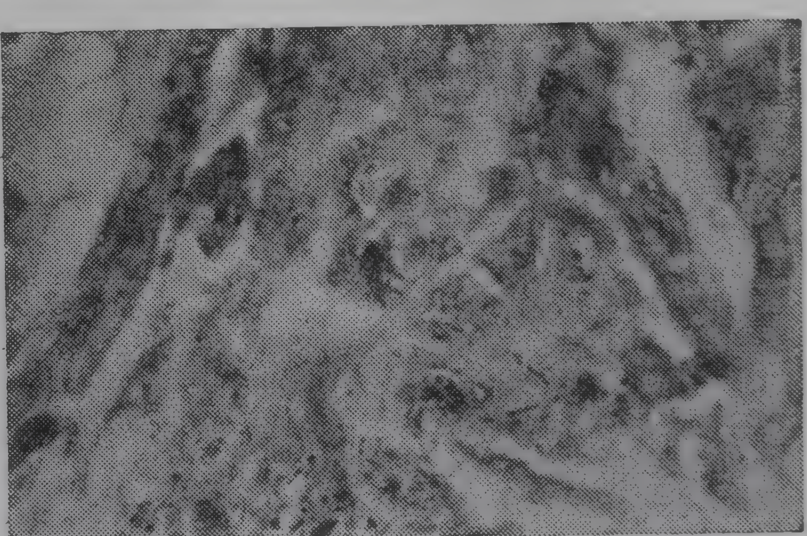

Figure 8. CCB Test with *M. leprae* in a lepromatous patient, showing large numbers of bacilli inside macrophages. Fite-Faraco stain, 40 X.

In any event, these experiments do indicate that the lack of inflammatory response and of cellular immunity against *M. leprae* in lepromatous patients come together with a marked deficiency in digestive properties

towards that bacterium and hence of defense against it.

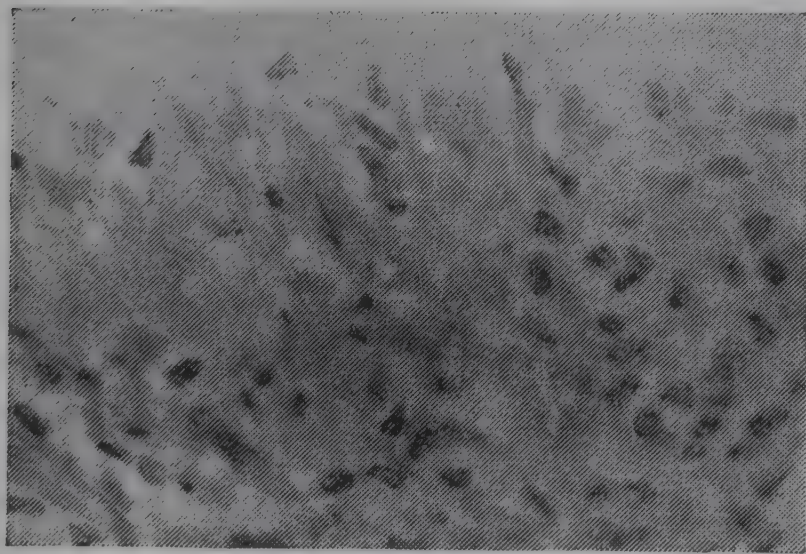

Figure 9. CCB Test with *M. leprae* in tuberculoid patient ; a tuberculoid granuloma with no bacilli can be seen. Fite-Faraco stain, 40 X.

With all these data a spectrum of clinical forms of leprosy may be visualized. These clinical forms correlate well with microscopic features and with cellular immune responses. Two polar types exist, the lepromatous and the tuberculoid. In the lepromatous pole there are widespread lesions affecting the skin, nerves and many if not most internal organs. Microscopically there is a granuloma formed by foamy histiocytes with no lymphocytes. Bacilli are present in great numbers inside histiocytes. The intradermal injection of bacilli does not produce a positive Mitsuda test and bacilli persist in situ for a long time. In vitro mitogenesis and lymphokine production is poor or non-existent when *M. leprae* is employed as elicitor. The clinical prognosis is poor and in principle, therapy should be given indefinitely. In the tuberculoid pole, lesions are single or few, they affect only the skin and peripheral nerves. Histologically there is a tuberculoid granuloma formed by epitheloid and giant cells with a goodly admixture of lymphocytes. Bacilli are very scarce. The intradermal injection of *M. leprae* induces a positive Mitsuda test and bacilli are disposed of in a relatively short time. In vitro mitogenesis and lymphokine production is active when *M. leprae* is used as elicitor. The clinical prognosis is much better and chemotherapy may be discontinued after clinical cure.

Intermediate forms exist between these two poles. The Madrid classification (8) recognized two such groups, borderline and indeterminate. The Riddley and Jopling classification (7) recognizes a greater number of intermediate forms (BL, BB, and BT) following the concept of "gradation" of microscopic, clinical and immunological features. For the purposes of this chapter it is enough to understand that features of intermediate groups lie between the two poles and that gradation of clinical and histopathological features is directly related to similar events in cellular immune responses and prognosis, including the length of time during which chemotherapy should be given.

It ought to be mentioned that the concept of "spectrum" does not mean that the disease in a given patient may travel through its whole range. In practice this is not so. BT patients, for instance, may worsen or improve but will not go into either the tuberculoid or lepromatous ends of the spectrum.

It is worthwhile to note that other intracellular parasitic diseases show similar "spectra" and correlations between clinical, microscopic and immune features and prognosis. American mucocutaneous leishmaniasis is a good example (3). Interestingly, patients with lepromatous leprosy show a normal response to Leishmania antigens and behave as others when infected with Leishmania. This is a further argument for the specificity of the immune defect in lepromatous leprosy.

In sum : Leprosy is a disease where different types and forms constitute a spectrum of increasing severity and stubbornness to therapy as one goes from the tuberculoid to the lepromatous pole. Increasing severity and poor prognosis are directly related to a progressive deficiency in cellular immune mechanisms, predominantly as it refers to response of T lymphocytes to *M. leprae* antigens. This may be studied by means of histologic techniques, intradermal testing and in vitro culture of lymphocytes. Current evidence favours the view that this lack of response (anergy) is specific and that deficiencies in other parameters, if they exist, are coincidental or secondary to a prolonged disease process. It is likely, but not certain that the defect lies primarily in the lymphocyte. The macrophage being an effector cell. It is not clear whether this defect is genetic in origin or acquired early in the life of patients.

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SPECIFIC SERODIAGNOSTIC TESTS FOR LEPROSY

MASAHIDE ABE

INTRODUCTION

The diagnosis of leprosy is usually based on clinical symptoms and bacteriological examinations. However, respective findings are not specific to leprosy, because similar skin lesions or peripheral nerve involvements are seen in other diseases and acid-fast staining of bacilli is a common property of various strains of mycobacteria. For these reasons, it is sometimes difficult to find out new cases in very early stage of leprosy and to prevent the onset of disease during the incubation period. Although the mode of leprosy infection is not clarified yet, it is generally accepted that some immune responses may take place before clinical manifestation of leprosy. Therefore, if an adequate method for detecting this response is available, early diagnosis of leprosy will become more reliable and it will bring much benefits to prophylaxis and treatment of leprosy.

IMMUNOLOGICAL BACKGROUND

1. Defense mechanisms in leprosy

When leprosy bacilli invade the body, they are first ingested in "phagocytes", the cells being known as monocytes or macrophages in various tissues and organs. After certain period of incubation in these cells, the bacilli may multiply to some extent. Thus, the phagocytes come to the end of their life and the bacilli released from dead cells are again taken in new phagocytes. During this repeated process, the product of living bacilli or the cell constituent of dead bacilli may act as "antigens" and stimulate immune sensitive cells (B-cells) which respond with the production of "antibodies". The antibodies are found as immunoglobulins in the serum and in various secretions. Generally, antibodies can combine specifically with antigens and precipitate soluble antigens or agglutinate particulate antigens. These reactions *in vitro* are the basis of serodiagnosis. The antigen-antibody reactions occurred *in vivo* may serve to localize, to neutralize and to eliminate hazardous antigens. There is another humoral defense mechanism called "complement system". This system consists of at least 15 kinds of serum proteins which are capable of interacting with each other, with antigen-antibody complexes, and with cell membranes. These interactions lead to the generation of various biological activities, such as lysis of bacteria, acceleration of phagocytosis, mediation of inflammatory processes. In leprosy, however, complement system seems to be useless for lysis of leprosy bacilli and rather to be favourable for their growth by accelerating phagocytosis. Thus, a series of these processes, antibody production, phagocytosis and bacterial growth, are repeated continuously and lead to the development of lepromatous leprosy.

On the other hand, there is a cellular defense mechanism which does not permit the growth of leprosy bacilli in phagocytes. This mechanism is called "cell-mediated immunity", the details of which will be described in separate articles. In short, the antigens released from leprosy bacilli stimulate another system of immune sensitive cells (T-cells). Activated T-cells are capable of proliferating in lymphoid organs, interacting with other cells, and producing chemical mediators which lead to the generation of various biological activities such as activation of phagocytes, inhibition of leucocyte-migration, damage of tissue cells, etc. When this type of immune response is working well, leprosy bacilli are destroyed by the activated phagocytes, and the amount of antigens relased from the bacilli is not sufficient for the stimulation of B cell system leading to the production of antibodies. These features are characteristic to tuberculoid leprosy.

2. Antigens of leprosy bacilli

Morphological components of leprosy bacilli are divided into 4 parts: cell wall, cell membrane, cytoplasmic particle and fluid. Main chemical component of cell wall is a complex of lipid, poly-saccharide and protein.

The other constituents are supposed to consist of one or more of these substances. Recently, a "halo-like substance" has been noticed by some investigators, but it is unclear whether this substance may be derived from bacilli or from host cells. Although chemical nature of antigens in leprosy bacilli is not clarified yet, it is reasonably possible to presume the major component of respective antigens by examining immune responses in leprosy patients and by searching some analogies with the antigens in tubercle bacilli.

(*a*) *Lipid antigens*

Two kinds of liquid, phospholipid and glycolipid are obtained from chloroform extract of lepromatous nodules[1]. The phospholipid, when adsorbed on kaolin particles, causes positive agglutination reaction with leprous serum, and this reaction shows good correlation with the agglutination caused by cardiolipin, a phospholipid purified from beef heart. This fact seems to indicate that cardiolipin or similar phospholipid may be present in leprosy bacilli. It is well known that cardiolipin is also present in tubercle bacilli.

The glycolipid fraction isolated from lepromatous nodules shows a specific inhibition of Middlebrook-Dubos' passive hemagglutination test using lipopolysaccharide antigen of tubercle bacilli. The principle of this serological reaction is as follows: when free antigens have combined with corresponding antibodies, the latter are no longer able to agglutinate red blood cells coated with the same or related antigens. Therefore, the above finding suggests that glycolipid fraction contains the antigens similar to those of tubercle bacilli.

(*b*) *Polysaccharide antigens*

The Middlebrook-Dubos' passive hemagglutination test is frequently positive with the serum of leprosy patients. The test shows a good correlation with the passive hemagglutination using water-soluble extract of leprosy bacilli. A polysaccharide fraction obtained from lepromatous nodule extract (NE) shows positive precipitation in agar-gels with rabbit antisera against BCG and the other mycobacteria. Similar antigens are also separated from leprosy bacilli grown in armadillos[2]. These facts seem to indicate that polysaccharides of these mycobacteria are antigenically common. Therefore, this antigen has little value for specific serodiagnosis of leprosy.

(*c*) *Protein antigens*

At least two kinds of protein antigens have been separated from water-soluble extract of lepromatous nodules (NE). These are tentatively called NEPR and NEG2[3]. The former has higher molecular weight and larger electric charge than the latter. Both antigens are capable of causing skin reactions in leprosy patients, the reaction being well correlated with the Fernandez' reaction and co-incident with the disease type. However, the antigenicity in rabbit is quite different; NEPR can easily induce the production of antibodies, while NEG2 does not. Rabbit antibodies prepared from anti-NE or anti-NEPR sera and labelled with fluorescent dye (FITC) can stain leprosy bacilli specifically. No mycobacterium other than this bacilli reacts with these fluorescent antibodies. On the other hand, rabbit fluorescent antibodies to respective mycobacteria do not react with leprosy bacilli after the absorption of cross-reacting antibodies by adding excess of polysaccharide antigens of respective bacilli. Therefore, NEPR is considered to be a specific protein antigen of leprosy bacilli.

Recently, for the purpose of skin reactions, protein antigens have been separated from leprosy bacilli grown in armadillos[4]. However, its serological properties are not known.

(*d*) *Antigens of insoluble components*

These are obtained by high speed centrifugation of sonicated bacillary suspension and they are the principal substances in lepromin causing Mitsuda's late reaction. The main chemical component of insoluble antigens may be a lipopolysaccharide-protein complex which constitutes the cell wall. The antibodies to this antigens are found in leprous serum by indirect fluorescent antibody technique.

PRACTICE OF SERODIAGNOSTIC TEST FOR LEPROSY

1. Necessary requirements as laboratory test

The most of serological tests are carried out by laboratory technicians. Although they should have mastered fundamental techniques for serological reactions, sometimes they misread the result of reactions because of unstable test reagents and/or unsuspected technical errors. Therefore, the technique of serodiagnostic test must be simple and reproducible as much as possible. The other important requirements are serological sen-

sitivity and specificity of the reactions. The former is expressed by the percentage of positive reactions in leprosy cases and the latter by the percentage of negative reactions in non-leprosy cases. Ideally, both of these percentages should be 100% or nearly 100%, but practically either of them has occasionally to be lowered in order to raise the other. For the purpose of screening suspected or doubtful cases, the test must be highly sensitive so that all of the cases in question are picked up. For the verification of leprosy and for the identification of leprosy bacilli, the test must be highly specific so that all of non-leprous cases are excluded.

Although numerous serological tests have been reported so far, the most of them are used for research purpose only and are considered to be inadequate for the above requirements. Only two tests which are worthy of being recommended as serodiagnostic test are described below, and it is very important to use these tests properly, according to the purpose of examination.

2. Outline of the method

(*a*) *Leproagglutination test*

This test has been developed in relation with serodiagnostic test for syphilis. It has been formerly known that the latter is frequently positive in the serum of leprosy patients. These biologically false positive reactions are due to the antibodies reacting with a mixture of cardiolipin and lecithin in 1:1 weight ratio[5], while syphilitic antibodies have highest affinity to those in 1:10 ratio. Therefore, using different ratios of cardiolipin and lecithin as antigens, differential diagnosis between leprosy and syphilis is possible. The reaction with the antigen of 1:1 ratio is called Leprogglutination.

The method of this test is briefly described as follows: one volume of alcoholic solution of cardiolipin and lecithin (each 0.5 mg/ml) is rapidly diluted with 19 volumes of saline, then mixed with 5 volumes of kaolin suspension in water (1 mg/ml). After incubation at 37°C for 30 minutes, the mixture is twice diluted with saline and is ready for use. This mixture is called antigen-particle suspension. The serum previously inactivated by heating at 56°C for 30 minutes is serially diluted to twofold with saline from 1:2 to 1:256 so that 0.2 ml of each diluted serum is left in each test tube. Two-tenth ml of the antigen-particle suspension is added to each tube and mixed well. After incubation at 37°C for 30 minutes, the test tubes are centrifuged at 2,000 rpm for 5 minutes. The agglutination is read by resuspending kaolin particles gently and scored as 3+, 2+, 1+ and 0 (negative), according to average size of aggregates. The agglutination titer is expressed by the highest dilution of serum showing 1+ positive reaction. This is called "L ratio titer".

For differential diagnosis of syphilis, similar agglutination test is carried out, using alcoholic solution of cardiolipin (0.01%) and lecithin (0.1%), 1:10 ratio instead of 1:1. The agglutination titer of this test is called "S ratio titer".

(*b*) *Indirect fluorescent antibody test*

This test is based on the same principle as that of fluorescent treponemal antibody absorption (FTA-ABS) test which is used for serodiagnosis of syphilis, and therefore called "fluorescent leprosy antibody absorption" (FLA-ABS) test. The details of the technique used for this test have been described previously[6]. In brief, the smear of leprosy bacilli is covered with the serum which has been absorbed and diluted by the addition of cardiolipin, lecithin and tubercle bacilli polysaccharide. After the absorption, the antibodies to these antigens are no longer able to react with leprosy bacilli and the sole antibodies reacting specifically with the bacilli remain in the serum. After reacting with the absorbed serum, the smear is rinsed in phosphate-buffered saline (PBS) to remove non-reactive serum proteins. The antibodies fixed to leprosy bacilli are detected by reacting with antihuman immunoglobulin antibodies labelled with FITC. As the latter combines with human antibodies, the leprosy bacilli in the smear show green fluorescence in a dark eye-field of fluorescent microscope. The antibody titer is expressed by the maximum dilution of absorbed serum giving positive reaction.

This test is very sensitive, that is, very suitable for detecting minute amount of antibodies irrespective of their immunoglobulin classes and of their immunological properties, because all kinds of antibodies capable of combining with the antigen of leprosy bacilli are concerned in the reaction. As the control, the smears incubated with fluorescent antibody alone should show no fluorescence. This test is rarely positive at 1:10 dilution of the serum from healthy non-contact. Therefore, the reaction at 1:40 or higher dilution should be considered to be positive.

(*c*) *Enumeration and identification of leprosy bacilli*

FLA-ABS test is useful for enumeration of bacilli or detection of bacilli-derived antigens in skin smears by using absorbed and diluted serum from known lepromatous patient, because bacterial index measured by this test shows a good coincidence with that obtained by routine test[6]. If the specificity of this reaction is confirmed by negative reaction with the smears of the other mycobacteria, the bacilli showing positive fluorescence may be identified as leprosy bacilli. For this purpose, direct stainings of bacilli with anti-NE or anti-NEPR fluorescent antibodies are also available, because these reactions are highly specific to leprosy bacilli, as described above. However, these antibodies are used for research purpose only, because their preparation has not been standardized yet.

3. Clinical significance

(*a*) *differential dagnosis of leprosy and syphilis*

In Leproagglutination test, both high titers in L ratio and S ratio are considered to be the complication of syphilis in leprosy patient. In fact, the other serodiagnostic tests for syphilis such as TPHA and FTA-ABS using treponemal antigen are also positive in these patients. Such cases were found, for example, in 43 (4.1%) among 1,038 cases of leprosy patients in Japan, the percentage being nearly the same as a prevalence rate of syphilis in this country at that time. If agglutination titer is high in L ratio, but low in S ratio, the latter means biological false positive reaction due to leprosy. In such case the reaction with treponemal antigen is always negative. A very strange and interesting fact is that no syphilitic skin lesion has been noticed in leprosy patients even if the complication of syphilis is confirmed by serological test. This may be due to the cross-immunity between leprosy and syphilis.

(*b*) *Correlation between Leproagglutination titer and clinical findings*

Leproagglutination (L-ratio) titer is closely related to the disease type of leprosy, except for the cases with the complication of syphilis. The titer is high (1:32 or more) in lepromatous leprosy, but low (1:16 or less) in non-lepromatous. The sera from healthy persons show positive reaction with low titer. Therefore, the reaction with low titer is not specific to leprosy. Positive reaction with high titer has clinical as well as immunological significance. The production of anti-cardiolipin antibodies in leprosy is supposed to be related to lipid-degeneration of lepromatous lesions (histologically expressed by the appearance of foamy cells). The isolation of cardiolipin-like phospholipid from lepromatous nodules as described above may support this hypothesis. As shown in Table 1, the cases with high titer are most frequent at retrogressive status of lepromatous skin lesion in which the appearance of foamy cells is predominant, secondly in progressive and least in quiescent status in which lepromatous lesion has been resolved. Relatively rapid increase of L ratio titer and its gradual decrease (a typical course of antibody production) were observed in many cases of lepromatous leprosy under treatment. Therefore, the change of antibody titer has prognostic value. In other words, continuous decline of L-ratio titer suggests the absorption of lepromatous lesion and a tendency to recovery. Conversely, progressive elevation or continuous high level of this titer suggests the progressive or active lepromatous lesion. When the extent of lepromatous skin lesions is graded as follows, L_1 represents the cases with the lesions existing in 4 areal units or less out of 16 made all over the body surface, L_2 ones with those in 5 to 11 units, and L_3 in 12 units or more. It is noticed in Table 2 that the cases with high titer tend to appear more frequently following the increase of lesions from L_1 to L_3. This is probably due to the fact that a patient with a greater extent of lesions will keep more leprosy bacilli and may produce the antibody more easily.

Leproagglutination titer seems to be closely related to the occurrence of reaction in lepromatous leprosy called ENL (*erythema nodosum leprosum*). As shown in Table 3, a case with ENL often shows a high titer. It is known that ENL occurs after the appearance of foamy cells. A rapid fall of L-ratio titer is frequently seen during ENL. These facts seem to support the etiology of ENL that it is an Arthus type of hypersensitive reaction caused by antigen-antibody complex formation in the foci and in the blood vessel. However, there is no direct evidence that anti-cardiolipin antibodies are concerned in this reaction. Be the etiology what it may, Leproagglutination test may be useful in foreseeing the appearance of ENL.

(*c*) *Significance of fluorescent leprosy antibody absorption* (*FLA-ABS*) *test*

The principal use of FLA-ABS test is to detect all kinds of antibodies capable of

combining with leprosy bacilli antigens. The antibodies reacting with cardiolipin-lecithin (1:1) and with tubercle bacilli polysaccharide are not concerned with this test, because these antibodies have been absorbed by the addition of excessive antigens. The effect of this absorption on the specificity of the reaction is shown in Fig. 1, by comparing average antibody titers before and after the absorption, using smears of various mycobacteria. In case of the reaction with leprosy bacilli (*M. leprae*), no significant fall of antibody titer is observed after the absorption, while statistically significant fall is noticed in case of the other mycobacteria. Therefore, the reaction with absorbed serum at an appropriate dilution is specific to leprosy bacilli. The antibodies concerned with this reaction are supposed to react with the specific protein antigen present in bacterial cytoplasm. However, further absorption of serum with NEPR, a purified protein antigen isolateed from lepromatous nodules, does not make the reaction quite negative, though the fall of antibody titer is distinct. In usual test, too, some bacilli show positive fluorescence of cell wall only. These facts seem to indicate the presence of antibodies reacting with the antigens of insoluble constituents.

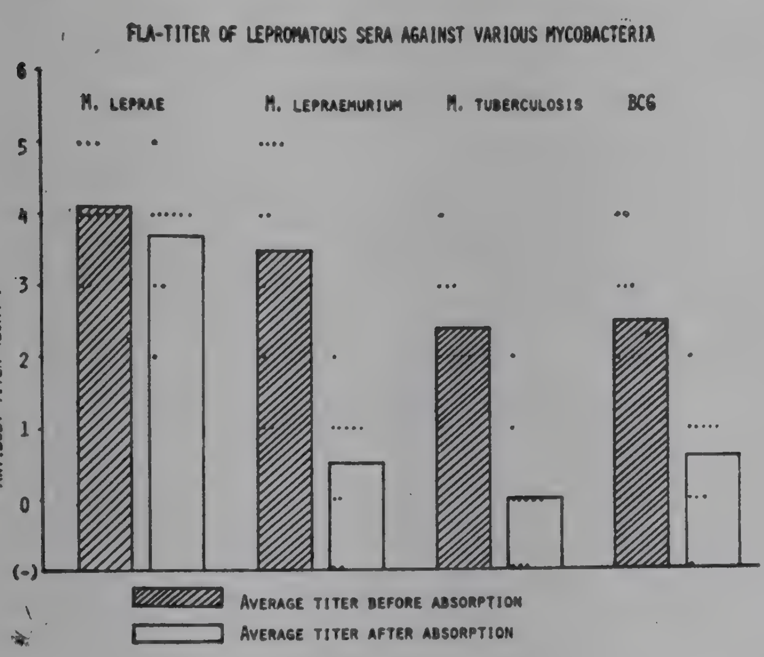

Fig. 1

FLA-ABS test is suitable for determining immunoglobulin class of antibodies by the use of fluorescent antibodies specific to respective immunoglobulins. For example, if anti-human IgG fluorescent antibodies are used instead of anti-human immunoglobulin antibodies, the former react selectively with IgG class antibodies fixed to leprosy bacilli. Therefore, the titer of these antibodies is easily determined. Using this technique, anti-*M. leprae* antibody titers of respective immunoglobulins were examined with the serum and nasal secretion from leprosy patients. The result is shown in Fig. 2. Solid line in the figure represents the mean of antibody titer and its confidence range in lepromatous cases and broken line is those in tuberculoid. The difference between these two means is statistically significant in case of total Ig and IgG antibody titers in the serum. Comparing with these titers, nasal IgG and IgM titers are very low in some cases of lepromatous patients and are negative in the other cases and in almost all of tuberculoid cases. Serum IgA antibodies are found only in 2 cases with lepromatous leprosy. However, nasal IgA antibodie sare found in all of the cases with tuberculoid leprosy and in 2 cases with lepromatous, though the titers are not high. IgE antibodies are entirely negative in the nasal secretion of all cases, but are found in the serum of 7 cases with lepromatous leprosy. Since IgA antibodies in secretions are known to have protective effect on the infection through mucous membrane, tuberculoid patients may be protected from the invasion of leprosy bacilli through this route.

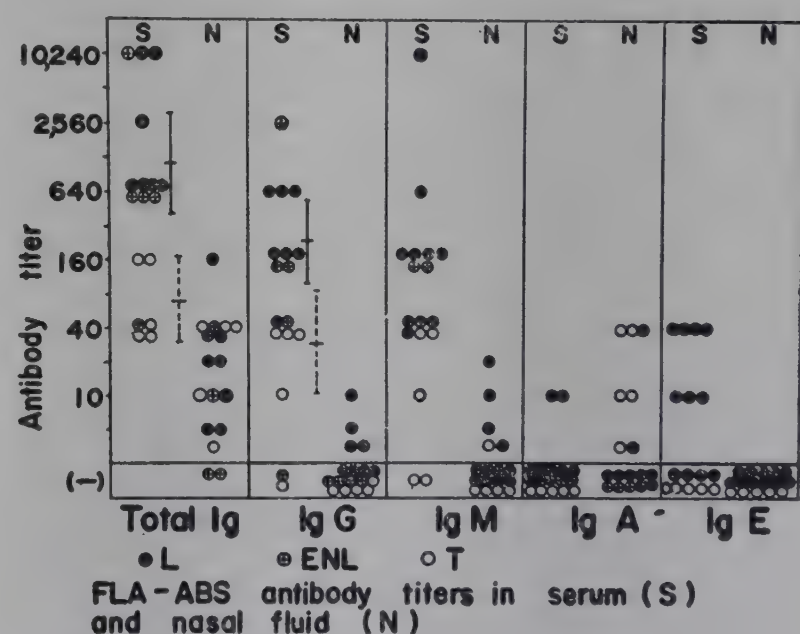

Fig. 2

The antibody titer in FLA-ABS test is closely related with immunological spectrum of leprosy expressed by Ridley-Jopling's scale. As reported previously[6], average antibody titer is highest in LL, declining from BL to BT, and lowest in TT. The relationship with the other clinical findings studies on the patients in Okinawa is shown in Table 4. The antibody titer is highest in progressive status of leprosy lesions irrespective of their disease type. Distinct fall of the titer is seen

in quiescent and arrested states. ENL has no definite effect on the antibody titer, in contrast to the difference in Leproagglutination test (Table 3). However, four cases with reversal reaction show high antibody titer, the difference from that of the other cases being statistically significant. Bacteriologically positive cases have higher titer than negative cases. From these results it is anticipated that FLA-ABS test may become positive in earlier stage of leprosy than that observed by leproagglutination test.

The usefulness of this test as an early serodiagnosis of leprosy has been stated in a previous report(6). This must be proved by testing large number of cases with indeterminate leprosy as well as contact cases. Among 19 laboratory workers in the author's institute 5 were positive (26.3%) in FLA-ABS test, though the titers were not high. Four persons out of 5 are working in the laboratory for more than 15 years. Accordingly, these positive reaction might be caused by subclinical infection by leprosy bacilli.

SUMMARY

For the practical, specific serodiagnosis of leprosy, the author recommended Leproagglutination and fluorescent leprosy antibody absorption (FLA-ABS) tests and discussed their immunological as well as clinical significances. The principle of Leproagglutination test is a passive agglutination of kaolin particles coated with cardiolipin-lecithin in 1:1 ratio (L-ratio). Simultaneously testing with cardiolipin-lecithin in 1:10 ratio (S-ratio), differential diagnosis of leprosy and syphilis is possible. The agglutination titer in L-ratio is closely related to the status and extent of lepromatous skin lesions and to the occurrence of ENL. Therefore, this test is useful as an indicator for the treatment of lepromatous leprosy. FLA-ABS test is based on the method of indirect immunofluorescence and capable of finding all kinds of antibodies reacting specifically to leprosy bacilli. This test is also useful for serological identification of this bacilli by using adequately absorbed and diluted serum from leprosy patients. The reaction is so sensitive that it becomes positive at very early stage after the infection. Therefore, this test may also serve for early serodiagnosis of leprosy.

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TABLE 1

Leproagglutination titer in relation to the status of lepromatous leprosy

Titer	Status			Total
	Progressive	Retrogressive	Quiescent	
High	64	407	38	509
(%)	(65.3)	(72.1)	(55.1)	(69.5)
Low	34	157	31	222
Total	98	564	69	731

TABLE 2

Leproagglutination titer in relation to the extent of lepromatous lesion

Titer	Extent of lesion*			Total
	L_1	L_2	L_3	
High	16	180	313	509
(%)	(24.2)	(66.7)	(79.3)	(69.5)
Low	50	90	82	222
Total	66	270	395	731

* Symbols L_1 L_2 and L_3 are defined in the text.

TABLE 3

Leproagglutination titer and erythema nodosum leprosum (ENL)

Titer	ENL		Total
	Positive	Negative	
High	294	215	509
(%)	(79.5)	(59.6)	
Low	76	146	222
Total	370	361	731

TABLE 4

Average antibody-titer of FLA-ABS test in relation to various clinical findings of leprosy

Clinical findings		No. of cases	Average titer	Difference	Level of significance
Status	Progressive	29	3.10	1.01	<0.05
	Retrogressive	46	2.09		
	Quiescent	22	1.00	1.79	<0.01
	Arrested	26	1.31		
ENL	Present	13	2.46	0.59	
	Absent	152	1.87		
Reversal reaction	Present	4	4.50	2.65	<0.01
	Absent	161	1.85		
Bacteria	Positive	39	2.54	1.21	>0.001
	Negative	73	1.33		

AN ANTI-LEPROSY VACCINE AS A LOGICAL APPROACH TO CONTROL OF LEPROSY

G. P. TALWAR

India has the world's largest number of leprosy patients. The official figures in 1970's are nearly twice as high as those of the 1960's. To some extent this increase may be a reflection of wider detection network. The surveys have, however, not covered every inch of the country and the actual number of patients suffering from this disease are likely to be higher than the 3.2 million official figures. This number is too large and their distribution too spread out to enable in practical terms, their isolation in sanitoria or other secluded places. The patients suffering from the Hansen's disease will therefore remain for a long time amongst us as a part and parcel of the general rural and urban community.

The disease has a latent period of several years and it is not infrequent that a case before its detection comes in contact with others with whom he lives and works. The infection is thus constantly spread by the untreated bacillus loaded cases of leprosy. The reservoir of the disease is probably the man, even though some animals such as the armadillo and mouse are able to offer a conducive environment for the growth and multiplication of the bacteria. These animals are however primarily of experimental interest and the major transmission of the disease may essentially take place from one human being to the other, either by direct contact, respiratory route or through vectors such as the bugs and mosquitoes. For an effective control and eradication of the disease therefore, this cycle requires to be intercepted. In other words situations have to be so devised that a human contact even when subjected to infection with *M.' eprae*, be capable of eliminating the bacteria and restricting the disease. This faculty is fortunately present in a large majority of us but is missing in some who may constitute less than 1% to about 8% of the total population in a given area. The task therefore is to find a way by which the defence capacity of the susceptible population can be reinforced. Concurrently, it will be of interest to learn the mechanism by which the naturally resistant large part of the population is able to combat the infection. These questions demand a comparative study of the status of the immune system in healthy men and in lepromatous leprosy patients.

Body defends itself against infections by a variety of ways. Skin offers a physical barrier and mucoid secretions, hair, cilia try to prevent the organism from gaining access into the system. When the entry takes place, polymorph leucocytes try to destroy the orgasisms nonspecifically by virtue of the deadly enzyme equipment that they possess. Other non-specific mechanisms such as the properdin and interferon also come into play with the general aim of eliminating the infection. All these offer the first-line defence to the invading bacteria.

In the event that the infection gains ground, and establishes itself, as is the case in the leprosy patients, it is necessary to consider the possible ways by which it happens. *M. Leprae* is an obligatory intracellular parasite and seems to grow in macrophages. These cells have an elaborate enzymatic machinery and can digest a variety of ingested material. Normally, these cells have a scavanger function and their role is to clear up the debris of bacteria and other organisms by engulfing these particles and digesting the same by the enzymes present in special sacs called the lysosomes. However, these very cells in some situations act as the host cells for *M. leprae* and the major question that arises is the reason why the bacteria are not eliminated by such cells in a patient suffering from lepromatous leprosy. Instead of killing and destroying the bacteria, the host cells in lepromatous leprosy patients provide a favourable soil and nutrition for growth and

poliferation of the bacteria. In patients who have self-limiting type of the disease (tuberculoid leprosy) e.g. who have good resistance to leprosy, the infection is localized and the bacteria eliminated (Fig. 1). The host cells function in these individuals in a manner so as to kill and digest the mycobacteria instead of supporting their growth. It is this differential way of handling the mycobacteria by different persons that requires close study. This knowledge would suggest rational ways to modulate the host cell function in the desirable direction.

What is wrong in lepromatous leprosy?

Lepromatous leprosy patients have high levels of globulins in the serum. They have also antibodies present in circulation which can react with *M. leprae* and other mycobacterial antigens (1, 2, 3, 4-7). The antibodies are apparently not protective against the infection. Their ability to form antibodies to TABC and other vaccines is unimpaired (8, 9). Humoral immune responses are thus operative.

On the other hand, the cell mediated immune functions are basically deficient in the lepromatous leprosy patients. This deficiency is both of specific and of nonspecific type. The blast transformation of lymphocytes with *M. leprae* antigens is poor (10, 11). They are unable to form the biologically active group of peptides (called lymphokines), when lymphocytes come in contact with *M. leprae* antigens (12-15). There is also evidence for a general depression of CMI (cell-mediated immunity) responses in patients with high bacterial load and is perhaps an instance of secondary immuno-depression consequent upon infection (16). The blast transformation of leucocytes with mitogens is depressed (17-20). The number of early rosette forming T-cells (thymus derived lymphocytes), carrying high electric charge is reduced. Some of these deficiencies are recovered with the clearance of the infection (21, 22, 23).

The impact of a deficient function of lymphocytes on cell mediated immunity and the handling by the macrophages of the ingested mycobacteria is only partially understood. Four years back we developed a system by which an adequate yield of monocytes was obtained from a reasonable amount of human peripheral blood (24). The monocytes developed into macrophages in suitable media supplemented with 40 percent of human AB-serum. The cells conld be maintained in culture for prolonged periods. They were active for engulfing mycobacteria and other particles. The cells could be loaded with *M. leprae* in *in vitro* conditions (Fig 2).

Sensitve methods were then devised to check whether in a given situation, the host cell would offer possibilities for the metabolic growth of the bacteria. A new method based on radioactive pulse with ^{3}H-thymidine was developed (25). The rationale of using radio-precursor was the absence in macrophages of thymidine kinase. The host cells were thus unable to incorporate this precursor. However, in the event that the bacteria divided, they must double their DNA content. The incorporated radioactivity counts in this system would thus primarily account for the bacterial DNA synthesis without interference of the host cells.

Preliminary experiments were performed by my coworker A. D. Krishnan (26), which shed some light on the possible role of lymphocytes in handling by macrophages of the ingested mycobacteria. It was observed that in case lymphocytes from tuberculoid leprosy patients were included alongwith the mycobacteria and macrophages in the culture system, the incorporation of ^{3}H-thymidine by the ingested mycobacteria is low. A similar experiment performed with lymphocytes from lepromatous leprosy patients showed a much higher incorporation of ^{3}H-thymidine (27). These observations suggest that the lymphocytes differ in their competence, and that it is the non-availability of the competent lymphocytes in the lepromatous leprosy patients which is perhaps responsible for the lack of the activated macrophage function and for the uninhibited growth of the bacteria in the host cell. (Table 1).

TABLE 1

Characteristics of the two polar forms of Leprosy

	Tuberculoid leprosy	Lepromatous leprosy
Bacterial Density	— or ±	++++
Lypmhocytes in the Lesion	+++	— or ±
Reactivity to *M. Leprae* antigens	+++	— or ±

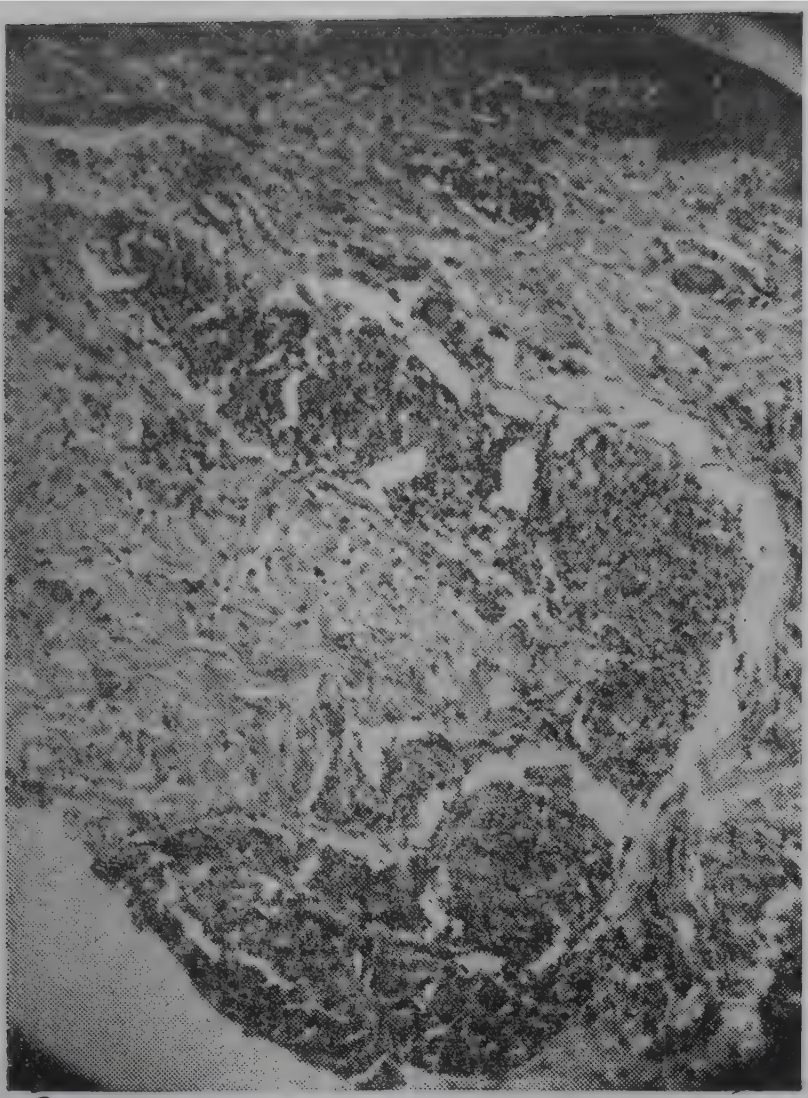

Fig. 1a. From a tuberculoid leprosy shows marked infiltration of lymphocytes and macrophages of epitheloid type. Scattered Langhan's type of giant cells are seen in the deep dermis.

Fig. 1b. From lepromatous leprosy patients, the lymphocytes (important indicators of immune reactions) are scanty. (H.E. × 100)

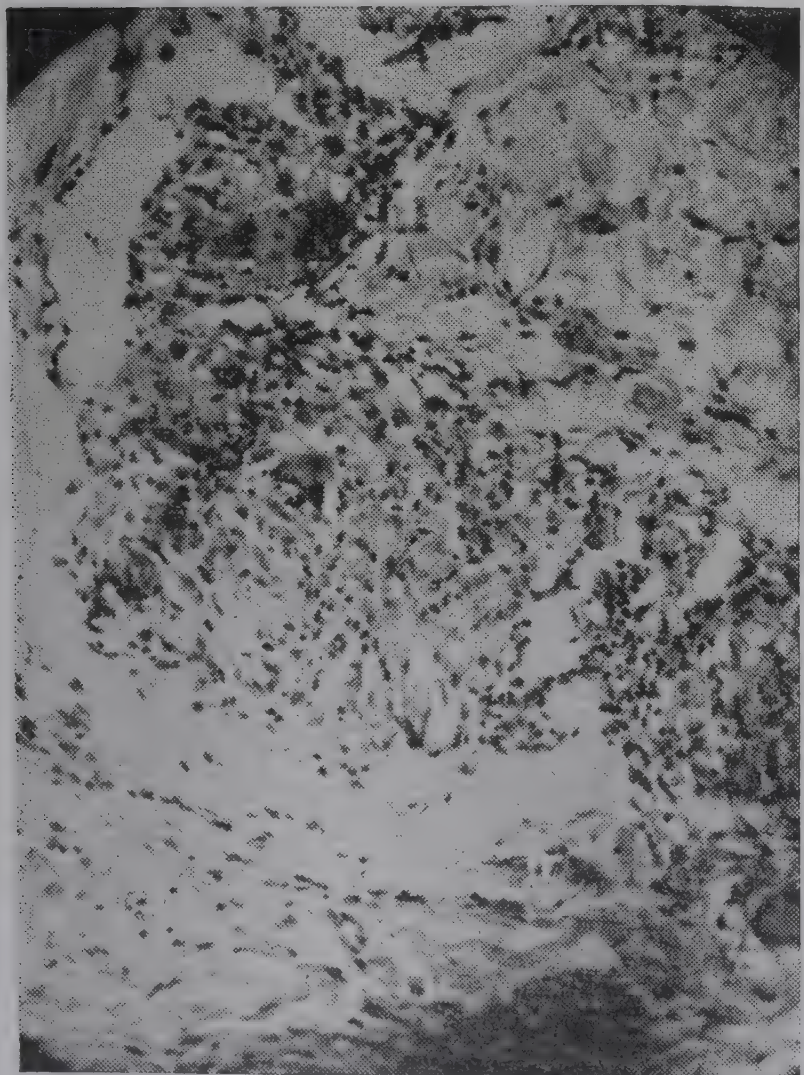

Fig. 1c. Tuberculoid granuloma characterised by giant cells and numerous lymphocytes at higher magnification (H.E. × 210).

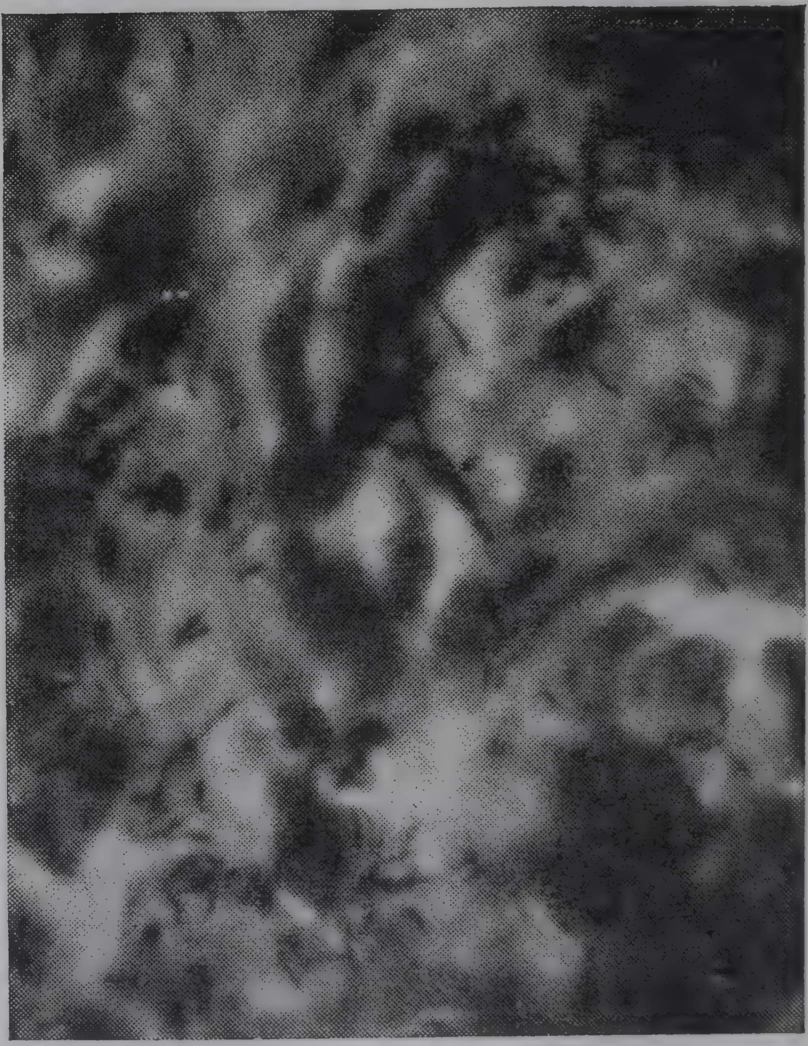

Fig. 1d. Histological appearance of the skin of lepromatous leprosy patient stained with Ziehl-Neelsen at higher magnification (X × 2100). Solidly stained bacteria can be seen in abundance in the 'foamy' histiocytes.

If these observations be true, then the basic task for the immunologists is to devise methods for improving the competence of lymphocytes capable of performing cell mediated immune functions.

Fig. 2 in vitro culture of macrophages derived from human blood monocytes according to Krishnan & Talwar (1974). The cells in culture can be infected with M. leprae and the influence of various factors such as competent lymphocytes and their products (lymphokines), as well as Drugs can be studied on Mycobacterial growth. Photo shows 2 cells loaded with bacteria. (X 2100).

A Vaccine

A vaccine needs to be developed which can improve the cell mediated immune functions in recipients. The vaccine should primarily invigorate the cell mediated immunity and not provoke the formation of antibodies, specially of the undesirable type which are non-protective.

The vaccine should be amenable to manufacture on a large scale, as the number of potential recipients will be large in countries where leprosy control is required. Moreover, the immunity imparted by the vaccine should be of a long duration.

M. leprae versus cultivable saprophytic mycobacteria as basis of the vaccine

Theoretically, it may be possible to prepare antigens from *M. leprae* which can impart immunity to *M. leprae* infection. This has indeed been achieved by Dr. Shepard *et al.* in mice (28, 29). The duration of immunity produced in such cases is, however, not known. From the experience gained with other mycobacteria (BCG in tuberculosis), it is known that for prolonged duration of immunity, recourse may have to be taken to live bacteria. BCG by itself may not be the right bacteria for an antileprosy vaccine. This experience has two lessons. On the one hand it encourages an approach with cultivable mycobacteria and shows the feasibility of the exercise. On the other it is clear that bacteria with better protective properties than BCG have to be used. Most experts feel that *M. leprae* has not been cultivated *in vitro* so far (although some investigators have reported cultivable forms—Bapat, Murohashi, Skinses, Chatterjee (30, 31, 32, 34). It is difficult to envisage the availability of attenuated strains of what may be generally acceptable as *M. leprae* without pathogenic potential. Immunization with *M. leprae* will therefore remain restricted to the use of killed preparations and no living vaccine with *M. leprae* is conceivable in the near future.

In contrast, a living vaccine can become a reality if we can find a suitable saphrophytic atypical cultivable mycobacteria. Atypical acid fast bacilli have been collected in clinics all over the world. Amongst these, those which are fast growing and nonpathogenic in the conventional test animals, need to be further probed for use as vaccines.

In our laboratory, a work on this line has been going on since that last 3 years. We have a collection of 71 mycobacteria. Out of these, the fast growers and non-pathogenic strains have been screened for the presence of the desirable antigens. The following strategy was employed for this purpose. Our aim was to select out those strains of mycobacteria which share the cell mediated immunity inducing antigens with *M. leprae*. We made use of tuberculoid leprosy patients whose sera and cells formed the reference points. The choice of the tuberculoid patients was based on the consideration that these patients have evidence of having had *M. leprae* infections and also of having had the requisite resistance to contain the disease and

an ability to eliminate the infections. A series of laboratory tests were performed with *M. leprae* and with other mycobacteria strains. Those showing close similarities with *M. leprae* with respect to CMI functions were selected out. The details of these laboratory investigations will be reported elsewhere in detail very shortly (33).

These were followed by confirmatory experiments in experimental animals in which the delayed hypersensitivity response of *M. leprae* and selected mycobacterial antigens was assayed. Protection experiments were also undertaken in mice.

These studies have led to the selection of about 5 strains of mycobacteria for further testing as basis of an eventual vaccine.

The next step requires a feed back from the field and the clinics. Mitsuda and Dharmendra types of lepromins prepared from *M. leprae* and from these strains of Mycobacteria have been distributed to a number of Centres for preliminary testing. The clinics engaged in this work are currently those headed by Dr. L. K. Bhutani, Head of the Department of Dermatology, All India Institute of Medical Sciences, New Delhi; Dr. Ratan Singh, Professor and Head of the Department of Dermatology, Maulana Azad Medical College, New Delhi; Dr. Gurmohan Singh, Professor and Head of the Department of Dermatology, Banaras Hindu University, Varanasi; Dr. L. M. Hogerzeil, Director and Specialist Dermatology, Victoria Hospital, Dichpalli, Nizamabad District; Dr. C. Vellut, Medical Superintendent, Hemerijckx Leprosy Centre, Polambakkam, Chingleput District and Dr. K. V. Desikan, Director, Central JALMA Institute, Agra. Others are expected to join and expand the trials with these preparations.

In case the feed back from these studies is positive and that one or more strains of mycobacteria turn out to be similar as seen by the patient vis-a-vis *M. leprae,* we would have come nearer to the development of a potential vaccine based on atypical Mycobacteria for control of leprosy. The advantages of using a cultivable mycobacterium will be the ease of its production on a mass scale and its relatively low cost.

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TREATMENT OF LEPROSY

S. B. ROY CHAUDHURY

Leprosy has been traditionally considered as an incurable disease because no effective drug was available against it. A variety of remedies have been tried from time to time but none of them have proved to be really effective against leprosy. These have icluded preparations of metals like gold, antimony, arsenic and copper, vaccines prepared from other mycobacteria and biological preparations like diphtheria toxoid.

In the early years of this century hydnocarpus oil (or Chaulmoogra oil) was "rediscovered" by the physicians treating leprosy. This oil, obtained from the seeds of *Hydnocarpus Wightina* has been used for a long time by practitioners of Indian Systems of medicine against leprosy and practitioners of modern medicine found that, unlike all the other remedies tried earlier, this was effective against leprosy. Hydnocarpus oil was widely used as the standard remedy for leprosy during the 20s, 30s and 40s, but after the introduction of sulphone it has gone out of use because of the manifestly superior results obtained with sulphones. Hydnocarpus oil (with 4% creosote) or ethyl esters of the oil (with 4% creosote or 0.5% iodine) was used as injections. These injections had to be given repeatedly for a number of years. Nowadays hydnocarpus oil is occasionally used by some practitioners as intradermal injections to restore colour in hypopigmented areas. It is interesting to note that recently there have been some reports that hydnocarpus oil does prevent to some extent the multiplication of *M. leprae* in foot-pads of mice.

SULPHONES

Dapsone (4, 4-Diaminodiphenylsulphone ; DDS) was discovered in 1908 by chemists working on dyes, but at that time its biological properties were not appreciated. About thirty years later when other sulfonamides were being tested against bacterial infections with great success, dapsone was also tried in the laboratory and was also found to be a strong antibacterial agent. Unlike the other sulphonamides, dapsone was found to be very effective against experimental tuberculosis. But the drug was too toxic for human use when used in doses similar to those of other sulphonamides. Several derivatives of dapsone were then tested and some of them proved to be less toxic but equally effective. Promine, one such derivative of dapsone, was first tried on leprosy patients in U.S.A. by Faget in 1941 with encouraging results. From that date began a new era in the treatment of leprosy. Subsequently, other derivatives of dapsone like Diasone, Promacitin and Sulphetrone which could be given safely by oral route, replaced promine which was expensive and had to be given intravenously. After about seven years of successful use of these derivatives, dapsone was tried in similar doses in order to reduce the cost of treatment still further. Oily or aqueous suspension of this drug was used initially as injections and subsequently dapsone tablets were used orally. The drug was found to be effective, practically non-toxic and treatment was also very economical. All these qualities have made dapsone the most widely used drug in the treatment of leprosy today. However, the disubstitute derivatives, diasone and sulphetrone, continued to be used in the management of patients who showed frequent reactions and were intolerant to dapsone. Subsequent studies showed that these derivatives exerted their action because they got broken-down in the alimentary tract to dapsone which was the parent chemical and patients with frequent reactions could tolerate these derivatives better than dapsone because only a very small quantity of the active substance, dapsone, was liberated from them. Therefore there is now no need to use dapsone derivatives in the treatment of leprosy.

Dapsone is effective whether given by mouth or by injections. The oral route is convenient as the treatment has to be continued for a number of years. Dapsone is absorbed almost totally from the gut when given orally and maximum blood concentration is reached

in about 3 hours. By 24 hours the blood concentration comes down to half the maximum level. Most of the drug is excreted in the urine, but small quantities are also found in the milk of the nursing mother. Dapsone is a bacteriostatic drug and it acts against *M. leprae* by interfering with the synthesis of folate compounds by competing with para-amino benzoic acid. Experimental studies have shown recently that dapsone has bactericidal activity also. Results obtained in the experimental animal indicates that a daily dose of 1 mg. dapsone for an average adult should be enough to give minimum inhibitory concentration in blood.

The World Health Organization Expert Committee on Leprosy in 1977 recommend a weekly maximum dose of 6 mg. to 10 mg. of dapsone per kg. body weight. The total weekly dose is to be given in the daily regimen, which means 50 to 100 mg. daily for an average adult and proportionally less for children.

It was customary to start the treatment with small doses of the drug and build up the dose graudally to the maximum in 4 to 6 months. But recent observations indicate that the size of the dosage has no influence either in the precipitation or in the severity of reactions. On the contrary very low initial dosage, interruption in therapy and low maintenance dose will only help in the emergence of dapsone resistant strain of *M. leprae.* Basing on these observations WHO Expert Committee in 1977 recommend that dapsone must be given in full dose, from the beginning.

Treatment should be continued without interruption in all types of leprosy till all clinical and bacteriological activity has subsided completely. Treatment should be continued with the same dose even after all clinical and bacteriological activity has subsided and the duration of treatment at this stage will vary according to the type of leprosy. In non-lepromatous leprosy treatment is continued in this manner for at least 1½ years, in Indeterminate type for at least 3 years and in Borderline and Lepromatous types for at least 10 years, or preferably for the rest of the life of the patient. This kind of maintenance therapy is necessary because the disease may relapse if treatment is stopped earlier.

In conventional doses, dapsone is not toxic. Sometimes haemolytic anaemia, hepatitis, nephritis or dermatitis may occur.. Large doses of dapsone may cause insomnia, psychosis or methaemogloginaemia.

Experience of the last 35 years has shown that sulphone is a very useful drug in the therapy of leprosy. About 3 years of dapsone therapy is adequate to cure an average non-lepromatous case and it takes about 5 years to make a lepromatous patient non-infectious.

Notwithstanding its proven benefit dapsone therapy has also certain limitations. Firstly, the rate of improvement slows down during the later stages of the treatment although initially the progress is quite rapid. Secondly certain percentage of lepromatous and near lepromatous cases show deterioration following an initial improvement under dapsone therapy. These cases were clinically suspected to be sulphone resistant and this was proved to be correct in 1964 by Pettit and Rees who demonstrated uninhibited multiplication of *M. leprae*, obtained from some of these cases, in the foot-pads of mice fed with dapsone. Subsequently workers from many parts of the world have reported the existence of sulphone resistant patients. These reports also suggest that the occurrence of sulphone resistance may be on the increase. Low dose of dapsone in the initial stages of treatment and iregular or interrupted treatment favour development of sulphone resistant leprosy. Thirdly, although dapsone has bactericidal effect, it is not possible to kill all the lepra bacilli in a patient's body with the use of this drug. Even after 10-12 years of therapy a very small number of bacilli can still be found in many lepromatous and near lepromatous patients. When treatment is stopped these bacilli multiply and in course of time cause relapse of the disease. These bacilli are not dapsone resistant but apparently they are able to persist without multiplication in spite of dapsone therapy. Because of this drawback dapsone therapy cannot be stopped and has to be continued indefinitely.

It can be seen from the above that treatment of lepromatous and near lepromatous leprosy patients with sulphone alone is not the ideal one. But so far no single drug has been discovered to be free from limitations and dapsone still remains the drug of choice in Leprosy Control Programmes. But we may have to supplement dapsone therapy with other drugs in the treatment of leprosy in order to minimize the possibility of relapse.

Acedapsone (4-4, Diacetyldiaminodiphenyl sulphone ; DADDS) is a recently introduced

repository sulphone available in oily suspension. It is injected subcutaneously or intramuscularly once in 75 days. The dose for an adult is 225 mg (1.5 ml) and for children under six years it is 150 mg (1 ml). In lepromatous patients improvement under DADDS therapy is reported to be comparable with that obtained with oral dapsone in conventional dosage. Although one injection of DADDS gives a constant blood level of DDS for 20 months, the blood level obtained with one injection of 225 mg corresponds to the level obtained with a daily dose of only 2 mg of dapsone and treatment with such a small dose, it is feared, may lead to the emergence of resistant strains of *M. leprae*. Therefore, till we know more about the long term effects of this drug it is not recommended for routine use.

LONG ACTING SULFONAMIDES

Drugs like Sulfamonomethoxine, Sulformetoxine, Sulfalene, Sulfadimethoxine have similar actions against *M. leprae* as that of dapsone. Some workers claim that these drugs are better than dapsone but others do not think so. Further, these drugs are expensive and are more toxic than dapsone.

THIOUREA COMPOUNDS

(i) *Thiosemicarbazone* : It is an antitubercular drug. Ryrie tried this drug in leprosy patients in 1950 and found it effective and several other workers have subsequently reported clinical and bacteriological improvement in all types of leprosy when treated with this drug. Some even reported complete restoration of sensation and regrowth of hair in affected areas along with the subsidence of the skin lesions. But the early improvement is not sustained in lepromatous leprosy and there is deterioration by the end of eighteen months of therapy, due to the development of bacterial resistance. The drug has been found to be useful in the treatment of patients intolerant to sulphone. In these patients, once the clinical condition is stabilised with thiasemicarbazone, it is possible to reintroduce sulphone in the therapy. The Madrid Congress in 1955 recommended this drug as an useful alternative for this group of patients.

The drug is given by mouth, 100 to 150 mg per day as a single dose, or in two divided doses. Minor side-effects like nausea, anorexia, mild headache, slight weakness and slight fall in total count of WBC, RBC and Hb level may occur in some patients. But these pass off when therapy is continued. Serious toxic effects like liver damage, drug fever and agranulocytosis are rare and are found in patients treated with large doses of this drug. Some workers have reported development of peripheral neuropathy in patients under long term thiosemicarbazone therapy. The drug should be discontinued in patients who develop such serious toxic effects.

(ii) *Thiambutosine* (Ciba 1906) : The WHO Expert Committee on leprosy in 1970 recommended this drug as a second line drug in the therapy of leprosy. Like thiosemicarbazone, thiambutosine is also a thiourea derivative. This drug is remarkable for its freedom from any toxic side effects. It can be given orally or parenterally, the maximum oral dose being 2 G once a day. The parenteral preparation is available as 20% suspension in oil for intramuscular injection,—10 ml (2 G) to be given as deep intramuscular injection once in a week or once in two weeks.

Both the above derivatives of thiourea have only a bacteriostatic effect on *M. leprae*. Their modes of action are similar and *M. leprae* resistant to one will be resistant to the other compound also. Early emergence of strains of *M. leprae* resistant to either of these compounds is common.

These drugs can be useful in the earlier phase of treatment of tuberculoid and borderline cases more prone to develop reactions, for reactions occur less frequently with these than with dapsone. These compounds can also be used with benefit in patients who are intolerant to sulphone. One of these drugs can be used as adjuvant in combined drug therapy.

PARA-AMINOSALICYLIC ACID

This drug has a bacteriostatic action against *M. leprae*. It has not been used much in the therapy of leprosy mainly because of high cost and it does not show any advantage over other drugs. Recent studies on experimental infection indicate that PAS partially antagonises the antimycobacterial action of dapsone. This point may be kept in view while planning the treatment schedule for leprosy patients who also suffer from tuberculosis.

ISONIÇOTINIC ACID HYDRAZIDE (Isoniazd ; INH)

This is a bacteriostatic drug and is effective against *M. leprae*. Though clinical improvement is found during early phase of therapy,

this is followed by deterioration by the end of six months of treatment because of emergence of resistant strains of *M. leprae*. Therefore this drug by itself is not suitable for treatment but it can be used with other drugs in combined drug therapy. Combining INH with dapsone has been reported to be beneficial in patients subject to chronic reactions.

INH is given orally and the maximum dose is 200 mg per day. Occurrence of peripheral neuropathy has been reported in patients who have had INH for a long period.

STREPTOMYCIN

This drug can be an useful adjuvant in the routine therapy of leprosy with dapsone because of its beneficial effect on the mucous membrane lesions and chronic sinuses of leprous lymphadenopathy. It is given as intramuscular injection, 0.5 to 1 g daily for a month or so.

CLOFAZIMINE (B663 ; Lamprene-Geigy)

Browne and Hogerzeil reported its anti-leprosy effect in 1962 and later in 1965, they also reported its usefulness in the treatment of lepra reaction. This information was received by leprologists all over the world with great relief, for, so far they have not had a drug having both anti-mycobacterial and anti-inflamatory properties ideally suitable for treating patients subject to frequent reactions.

Clofazimine is a Rimino-phenazine dye available as dark red crystals. It is given orally and is absorbed slowly from the gastro-intestinal tract. Absorption is better when given as micro-cystals suspended in oil or wax and the drug is marketed as such in gelatin capsules. After absorption the drug is taken up by the reticulo-endothelial cells in all the organs and retained there in crystalline form. Excretion from these depots is slow, and it is excreted in the urine, sebum, sweat and also in the milk of the nursing mother.

Clofazimine is a bacteriostatic drug which acts by interfering with the bacterial nucleic acid metabolism. Experimental study shows that the drug also possesses bactericidal property. The anti-bacterial action of clofazimine is equal to that of dapsone, but the drug is unique in the therapy of leprosy because of its associated anti-inflammatory effect and so its usefulness as an anti-reaction drug. Patients treated with clofazimine do not usually develop severe reactions.

Under clofazimine therapy clinical improvement and improvement in bacteriological and morphological indices are comparable with that obtained with dapsone. According to a few workers there is quicker clinical and bacteriological improvement and striking improvement in neurological function in patients under clofazimine therapy.

Clofazimine has both anti-leprosy and anti-reaction effects and so is the drug of choice in the management of patients having frequent reactions and have become corticosteroid dependent. Therapy in these patients is started with a high dosage of clofazimine, like 100 mg two to three times a day, which is continued for six to eight weeks and is then reduced to 100 mg daily for a period of another three months. In patients with moderate to severe reactions it will be necessary to introduce other quick acting anti-reaction drugs like steroids in the beginning of clofazimine therapy. These can be stopped later, after clofazimine starts to exert its anti-reaction effect, which takes about four to six weeks from the day of its introduction. Once the patient's reaction is under control, dapsone can be reintroduced in the therapy under cover of clofazimine. Clofazimine can be withdrawn after a total period of five to six months, in most patients, without recurrence of reaction. If desired clofazimine may be continued as an antileprosy drug at the reduced dosage of 100 mg twice a week along with dapsone.

The dosage schedule of clofazimine as an antileprosy drug has not yet been standardised. It is tentatively suggested that in the treatment of lepromatous and borderline cases the drug may be given as 100 mg daily for 6 months followed by 100 mg twice weekly for indefinite period. The drug is more commonly used in the above dosage schedule, along with routine dapsone therapy. Clofazimine has proved useful in the management of sulphone resistant cases.

The greatest drawback of clofazimine therapy is the discolouration of skin and conjunctiva. The skin becomes reddish after clofazimine therapy and the colour gradually deepens to blackish-brown ; the skin also becomes dry and scaly (ichthyotic). These changes are more prominent in the areas of leprosy lesions than in the normal skin. Sometimes the patient complains of itching sensation. The oral mucosa, urine, stool and sweet also show red colouration. Serious complications like diarrhoea and gastro-

intestinal cramps have been observed occasionally in patients getting high doses of clofazimine. Clofazimine cannot be considered for the routine treatment of leprosy because of its high cost and the side effects mentioned above.

RIFAMPICIN (or Rifamycin RMP)

The observation in 1972 by Shepard and his co-workers that no viable bacilli could be detected in the tissue of lepromatous patients within a few days of institution of refampicin therapy has made rifampicin the most promising drug in the therapy of leprosy, because it can render even a highly infectious case non-infectious within few days. But it is now known that a few viable bacilli can exist in the tissues of patients who have had rifampicin for even as long as five years.

Rifampicin is a semi-synthetic derivative of Rifamycin-S.V. Peak blood level is reached in 2 hours after oral administration and bactericidal concentration is maintained for 15 hours. The effective blood level is maintained for few days after a high dose as the drug is excreted in the bile and gets re-absorbed from the gut. Studies in experimental infections show that the drug has a strong bactericidal activity against *M. leprae* by inhibiting the synthesis of bacterial RNA. The drug is excreted mainly in the bile and urine.

Clinical improvement becomes apparent in lepromatous cases under rifampicin therapy from the second week onwards, initially in the lesions of the mucous membrane, and by the end of three months all round improvement is achieved. A rapid fall in morphological index in the skin smears is the most striking feature after rifampicin therapy. Morphological index falls to zero in skin smears and histological sections by the end of three to four weeks of treatment. Although the fall of MI is rapid, the fall in bacteriological index is not quicker than with dapsone.

Because of its high cost rifampicin has been used so far in the treatment of sulphone resistant cases and in bacilliferous forms of leprosy either as a single drug or along with other drugs like dapsone and clofazimine. In the trials conducted by different workers, the dosage of rifampicin has varied from 150 mg to 1200 mg and the treatment schedule has varied from single administration to daily or periodical administration of the drug upto a total period of 5 years. The results of these studies confirm the findings of experimental work that rifampicin is a very effective anti-leprosy drug. However, the optimal dose and the duration of therapy required for treating a patient of leprosy are still to be determined.

Rifampicin is toxic to the liver and it may cause gastric disturbances like nausea, loss of appetite and vomiting. The serious toxic effects with rifampicin like thrombocytopenia, purpura, anuria and fever with arthralgia ("Flue syndrome") are rare. The serious toxic effects are due to formation of antibodies to rifampicin and were observed in tuberculosis patients who were intermittently given high doses of this drug.

As indicated earlier rifampicin is an expensive drug and cannot be used as a routine drug for leprosy ; but the drug possesses strong bactericidal action and it will be a very useful adjuvant in the combined drug treatment of lepromatous and near lepromatous patients. Rifampicin is available in the market as capsules of 150 mg and 300 mg.

ETHAMBUTOL, ETHIONAMIDE and PROTHIONAMIDE

These antitubercular drugs have come into prominence in recent years in the therapy of leprosy as these were found to be effective against *M. leprae* also. Moreover, in experimental infection they were found to potentiate the action of each other and exert additive effect on *M. leprae* when these were used along with dapsone, rifampicin or clofazimine.

These drugs are recommended as useful adjuvants in combined drug therapy and they are not suitable for use as a single drug in the treatment of leprosy.

COMBINED DRUG THERAPY

The ideal drug for leprosy should be capable of producing quick and lasting clinical and bacteriological improvement, it should not induce reactions or other complications and after stopping treatment the disease should not relapse. No such drug exists. Therefore it is now felt that one should use a combination of drugs in the treatment of leprosy, especially in lepromatous and near lepromatous borderline cases, instead of relying on one drug alone. This should help to destroy the bacilli more rapidly and more completely so that emergence of resistant

strains of bacilli is avoided and relapse of leprosy is also prevented. Several drug combinations are being tried and promising results are being reported. This subject is dealt with in greater detail elsewhere in this volume.

IMMUNOTHERAPY

In lepromatous and near lepromatous leprosy the patient not only harbours an enormous number of bacilli but he also lacks immunity and because of this there is an unusual delay even in the elimination of dead bacilli from the patient's body. As the immunological processes help in the destruction of bacilli and their elimination it may be expected that an improvement in the immunological status will make chemotherapy more effective in these patients. This is being tried now and some workers claim to have achieved transient lepromin positivity and quicker clinical, bacteriological and histopathological improvement in lepromatous patients after transfusion of dialysable transfer factor or leucocytes from lepromin positive normal persons or from patients having tuberculoid type of leprosy. At present this type of treatment by attempting to change the immunological state of the individual should be considered purely as experimental.

TREATMENT OF REACTIONS IN LEPROSY

G. RAMU and C. G. S. IYER

Introduction

"Reactions" or Episodic exacerbation of lesions during the course of leprosy are encountered in tuberculoid, borderline and lepromatous types of leprosy. Certain provocative factors are known to precipitate reactive episodes, such as: (a) concomitant infections i.e. malaria, filaria, septic conditions, intestinal infections and worm infestations (b) debility following acute illness like chicken-pox, small-pox, typhoid etc. (c) physical, physiological and psychological stress (d) small-pox vaccination, TAB vaccination, tuberculin testing (e) excess of 'hot food' or alcohol (f) certain drugs especially injudicious and excessive antileprosy therapy, sulphonamides, potassium iodide, hetrazan etc. Certain salient clinical characteristics of these reactions are given below:—

1. Acute exacerbation in the tuberculoid cases is characterised by pronounced increase in the redness and swelling of the lesions with increase in extent, oedema in and around the lesions and rarely ulceration in the lesions. Painful swelling and tenderness of regional and cutaneous nerves is very often found and cold nerve abscesses may occur. Paralysis of muscle groups supplied by the involved nerve trunk are common.

2. Reaction in borderline leprosy may vary from mild exacerbation of skin lesions to moderate forms with the appearance of numerous pleomorphic skin lesions, lesional oedema, oedema of hands and feet and to the severe forms with pronounced constitutional symptoms, neuritis, arthritis and rarely visceral involvement. Multiple paralytic deformities may be seen and there is a tendency to assume the lepromatous form in the BL cases.

3. Reaction in lepromatous leprosy is characterised by pronounced constitutional symptoms, acute inflammation of existing skin and mucous membrane lesions and occurrence of erythema nodosum leprosum, (ENL), subcutaneous nodules, pemphigoid, pustulating and ulcerating lesions. Other manifestations include neuritis, arthritis, orchitis, renal and supra-renal involvement, iridocyclitis, lymphadenopathy, hepato-splenomegaly etc. Tendency to recurrent reaction is observed in 14% of cases in whom reaction occurs. (Ramu and Ramanujam, 1964). Lepra-reactions increase the morbidity of the disease and endangers life in a certain number of patients. Non-paralytic deformities of the hands and feet occur from contractures resulting from deep seated inflammation under the skin as well as arthritis of small joints.

The varied clinical manifestations of reactive states in leprosy are essentially expressions of two types of immunological responses.

Tuberculoid reaction represents an intense cellular hypersensitivity which is a major cause of nerve damage.

Alterations in cellular immunity in the immunologically unstable Borderline Spectrum may result in a condition with many features of tuberculoid reaction and associated with severe neuritis. This has been called an upgrading or reversal reaction. On the other hand there may be a depression of the cellular immunity with a shift to the lepromatous pole, termed as a down-grading reaction.

The lesions of reactions in lepromatous leprosy arise due to deposition of immune complex (antigen, antibody and complement) at various sites. Such a deposition in the skin is manifested as ENL.

Treatment of acute "Mild" reaction in lepromatous leprosy

This condition manifesting a few evanascent ENL and with a rise of temperature below

100° F Calls for simple analgesic drugs like paracetamol 120 to 320 mg. twice a day or aspirin 300 mg. twice a day; the patient is advised to continue the specific antileprosy treatment and avocation. If the patient does not improve, he is put on an antimalarial i.e. Chloroquin Sulphate 1 tablet twice a day.

Acute reactions of moderate intensity

The patient has a rise in temperature above 100° F with inflammatory skin lesions over the extremites or trunk and face.

General

The patient is advised rest; painful condition like arthritis, neuritis etc. are treated with aspirin or paracetmal. Anti-reaction drug, chloroquin phosphate e.g. resochin or avloclor is given in a dose of 1 tablet 3 times a day till the fever subsides and later 1 tablet twice a day for 2 weeks or till the inflammatory lesions subside.

If in a week's time the desired therapeutic response is not obtained the patient should be changed over to treatment with an antimony preparation. In a hospitalised patient, this treatment can be started straight away. PAT (Potassium Antimony Tartarate, a trivalent compound) is administered by I.V. route in a dose of 0.02 gm. for 3 injections and later 0.04 gm. on alternate days for 3 more injections in the form of a freshly prepared 2% solution in 10 ml. of normal saline or along with calcium gluconate 10%, 10 cc. Extravasation of the drug outside the vein causes inflammation and sometimmes necrosis. Under situations where PAT cannot be used e.g. lack of fresh solution, in children, and in the field, the trivalent compound (fantorin) may be used in a dose of 2 cc. intramuscularly of a 6% solution on alternate days for 6-10 injections.

Sodium Antimony gluconate (a pentavalent compound) available as stibatin, stibonate, or as such can be administered by the intramuscular route every day in a dose of 3-6 cc, upto a total of 40-60 cc. To avoid hypersensitivity reactions to antimony an initial dose of 1 cc. is given followed by 2 cc, if no hypersensitivity reactions are detected.

Dapsone Therapy

The specific treatment may have to be halved or temporarily suspended if the reaction is not controlled.

Acute 'Severe' Reaction

In this form, the temperature rises above 102° F and the inflammatory skin lesions are extensive possibly with pustulation. Management consists of:—

(i) Complete rest in bed.

(ii) Careful nursing.

(iii) Suspension of antileprosy treatment.

(iv) Reassurance.

(v) Use of tranquilisers, antipyretics and analgesics.

(vi) In the absence of anemia, renal involvement or low blood-pressure antimonials may be considered as basic therapy as mentioned earlier. When the routine therapy fails, corticosteroids should be used. Corresponding dosage of prednisolone, triamcinolone, beta or dexamethasone is given once a day. An initial 20 mg. of predmsoline or the corresponding dose of any of the analogues is given. If response is poor, the dose may be increased by 10 mg. given as another dose. Where life is imperilled the initial dose should be large. In the once a day regimen, depression of the suprarenel is reported to be less likely. When a favourable effect is apparent the dose is tapered off gradually by taking off one tablet in every 4th or 5th day and continued even after there is amelioration of symptoms for about a week.

Pustulating & Ulcerating lesions

For pustulating and ulcerating lesions the treatment has to be supplemented with antibiotics, commonly penicillin or strepto-penicillin, even though pyogenic organisms have not been isolated from the lesions. Chloramphenicol has an additional advantage of being immuno-suppressive.

Recurrent lepra reaction or chronic reaction

The basic measures consist of administration of an antimalarial drug (Chloroquin) at first in adequate doses to control the reaction and later in the reaction suppressive dose of 1 tablet daily supplemented with INH 100 mg. INH has some antileprosy activity and does not usually provoke reaction.

Chloroquin toxicity includes besides malaise, head-ache and vomiting, ocular

complications like corneal opacities and sometimes irreversible retinopathy and rarely neuromyopathy. Fortunately, corneal opacities and retinopathies clear on suspension of treatment and neuromyopathies are known to occur if the treatment is continued for more than a year. When the patient is free from reactive episodes, dapsone is introduced in 1 mg. dose once a week. At periods as judged by the patient's response, commonly fortnightly, the dose is administered on alternate days and still later daily. The dose is further increased after long stages to the maximum tolerated dose. It has been observed that even such small doses as 1 mg. to 5 mg. daily are definitely effective in improving the clinical condition and a concurrent fall in bacteriological status. However, the aim should be to increase the dose to adequate therapeutic doses and not to be complacent with the improvement as recrudescence of activity of the disease has been seen in a few cases who had earlier registered stisfactory progress.

Therapy of cases with recurrent pustulation

In these cases, the use of a long acting sulphonamide eg. sulphadimethoxine (Madribon) administered in a dose of 0.5 gm. daily has been found to be of value in controlling and preventing the recurrence of pustulating skin lesions. This has also been of some benefit in reducing the attacks of arthritis. The rationale behind the use of antibiotics or sulphonamide is that these lesions seem to be monitored by a focus of streptococcal infection somewhere in the body since in a certain percentage of cases antisterptolysin titres are found to be high.

Therapy of cases with repeated steroid dependant lepra reaction

In these cases the introduction of Thalidomide and Clofazimine has considerably altered the prognosis. Both Thalidomide and Clofazimine in a dose of 300 mg. daily are useful in dealing with recurrent lepra reaction. While Clofazimine therapy generally takes 6-12 weeks to control the reactive state, Thalidomide does so in a much shorter time (Iyer and Ramu, 1976). Both the drugs possess the property of not only controlling the occurrence of reaction but also enables the weaning of patients from steroid dependence and increase their sulphone tolerance.

The therapy with these drugs consists of two parts: The first part consist of giving a dose of 300 mg. of either of the drug till the reactive states are completely controlled; i.e. 6-12 weeks with Clofazimine and 3-5 weeks with Thalidomide. During this time the dose of steroid is tapered off and the drug stopped finally. During the second part DDS treatment is inducted and built upto optimum levels, the dose of Thalidomide and Clofazimine is gradually reduced till the patient is on a maintenance dose of 50 mg. of Thalidomide or 100 mg. of Clofazimine on alternate days.

In trials conducted in Chinglepet, Clofazimine was found to confer fairly lasting freedom from reaction after stopping the drug after a year. Cases on Thalidomide on the other hand relapsed into the reacting state soon after stopping the drug. A maintenance dose of Thalidomide has therefore to be continued till bacterial negativity has been achieved. (Hastings at al 1970).

Drawbacks of Thalidomide Therapy

Thalidomide, a cyclic imide (N-Pthalidimidoglutarimide) was accidentally discovered to have reaction suppressing properties by Sheskin (1965). The therapeutic efficacy of thalidomide as an antireactive drug has been reported by several workers and in a W.H.O. co-ordinated trial (Iyer at et 1971). But it has to be emphasised that the control of severe reaction is not as efficient as with corticosteroids and therefore it cannot replace steroid in severe reaction.

2. While drowsiness, loss of appetite, asthenia, loss of erection, dryness of nasal and oral mucosae and bradycardia are minor side-effects of the initially big doses, its embryotoxic properties prohibits its use in women in the child bearing age.

3. Thalidomide neuropathy is a known toxic effect (Crawford, 1969) through not reported often.

4. Rebound phenomenon on stopping the treatment in recurrent reactional cases is as common with Thalidomide as with corticosteroids.

All these however do not detract its use in recurrent reactions in sulphone intolerant, steroid dependent cases.

Side effects of Clofazimine therapy

The use of Clofazimine, a riminophenazine drug first reported by Browne (1965) combines anti-inflammatory properties (Vischer, 1969)

with bacterio-static effect on *M. leprae* (Shepard, 1969).

Though the drug exerts a definite control on reaction yet its action is slow: therefore in acute painful manifestations cortico-steroids have to be used in combination with it to get over the acute phase.

While the tendency to recurrence of reaction is reduced after prolonged therapy due to depots of the drug being built up in the tissues, red and black pigmentation and ichthyosis are common side effects. Gastro-intestinal disturbances may be particularly severe sometimes simulating acute abdomen. Female patients seem to tolerate the drug rather poorly. A lower dose of the drug in women, hydration therapy followed by application of vaseline or lanolin for ichthyosis are advised. Isonicotinic Acid hydrazide 100 to 200 mg. daily appears to favour mobilization of tissue Clafazimine and minimise side effects (Ramu and Iyer, 1976).

Thalidomide and Clofazimine are useful in dealing with immune complex induced reactions eg. lepra reaction and are not of value in cell mediated reactions.

Treatment of certain manifestation of lepra reaction: Treatment of acute painful neuritis

In addition to the treatment of reaction, local application of heat in the form of hot compresses or diathermy, simple warmth by warm wrapping and splinting the part with the nerve in the relaxed position helps in alleviating the pain; cooling of the skin over the painful stretch of involved nerve by spraying ethyl chloride relieves the pain and can be repeated two or three times daily. Perineural injection of novocain and a vasolidator drug eg. ½ ml. of novocain and 2 ml. of isoxuprine hydrochloride (duvadilan) or tolazoline hydrochloride (priscol) is found to relieve this distressing condition. Nicotinic acid 100-250 mg. twice a day after food administered routinely is useful in cases prone to develop neuritis. Injections of vitamins B12, B1, and B6 have been routinely employed empirically. As inflammatory oedema may be the cause of pressure on nerve fibres and consequent pain; acetzolamide or a thiazide compound given as a single dose in the morning is of benefit. In acute nerve palsies, the limb is splinted in the functional position followed by exercises. In multiple painful neuritis recourse has to be taken to cortiosteroid therapy; in steroid dependent recurrent reactions where the predominent manifestation is painful neuritis thalidomide is of decided value.

Acute Eye Manifestation

A red painful eye in lepra reaction suggests ENL in the bulbar conjunctiva, sclertis, and/or iridocyclitis. Patient should have an eye shade, boric fomentations and the pupil kept dilated with 1% atropine drops or ointment. Intra-ocular tension should be tested and if found high, diamox should be used. Steroid therapy is indicated in iridocyclitis when the vision is imperilled. The use of non-steroid anti-inflammatory drugs like phanylbutazone, oxyphenazone or indomethacin gives gratifying results.

Arthritis and periostitis

In addition to therapy of reaction application of local counter irritant in the form of ichthyol glycerine paint and wrapping the joints with a layer of cotton wool gives some relief. Short wave diathermy is useful. Non-steroid anti-inflammatory drugs eg. aspirin, phenylbutazone and indomethacin might be of use. Cases with recurrent arthritis become steroid dependent; while Thalidomide might be of use in some cases, results are not uniformly good.

Orchitis

Painful orchitis needs to be treated with local warmth and application of 10% ichthyol glycerine. Repeated orchitis can lead to gross destruction of testes and contributes to the development of gynaecomastia. Anti-reaction treatment has to be prompt and efficient.

Reaction hand

Deep seated inflammation in the cutis during the acute phases of lepra reaction gives rise to a painful swelling of the hands (Ramu and Ramanujam, 1964). During this phase, treatment consists of splinting the hand in the functional position and keeping the limb elevated and the use of a thiazide diuretic. Following on the heels of 'recurrent' attacks of 'reaction hand', contractures develop, the skin becomes thick, fibrotic, inelastic and pulls the fingers in different directions to produce a bizarre deformity (Ramu and Ramanujam, 1964). In early contractures injection of a depot corticosteroid along with hyalase locally twice a week accompanied with physiotherapy may be of help (Ramu, 1967).

Renal involvement

Oliguria, soft pitting oedema, albuminuria and microscopic or macroscopic haematuria

characterise the renal complication of lepra reaction. Patients should preferably be hospitalised for providing rest and nursing, the fluid intake and urine output measured and fluid intake adjusted accordingly. Adequate quantity of glucose, bread, milk and fruits should be given. Antimonials must be avoided, antileprosy treatment stopped and prompt steroid therapy instituted.

Supra renal involvement

Insufficiency of the supra-renals may suddenly occur during reactive states in lepromatous leprosy. This is characterised by a profound fall in temperature and blood pressure below basal levels with dehydration, hypoglycaemia and increased serum potassium levels. This condition calls for prompt treatment with adequate quantity of glucose and normal saline upto 5% of total body weight in 24 hrs., i.v. injections of hydrocortisone hemisuccinate 100 mg. may be followed by intramuscular hydrocortisone hemisuccinate 25 mg. every 8 hrs. Following recovery oral corticosteriod therapy in adequate doses is given and gradually tapered off.

Management of Borderline reaction

The reactive state in borderline leprosy may be very severe in a certain number of patients. There may be considerable oedema in the lesions and extremities, multiple nerves may be acutely swollen and painful with impending paralysis. While the drug treatment of mild reaction with antimalarials and antiomonials is adequate, in severe reactions with multiple neuritis and impending paralysis, corticosteroid therapy is mandatory to avoid crippling deformities.

Diuretics (Thiazide) are useful to eliminate the oedema fluid from the lesions, the limbs, as well as from the nerves.

Another indication for the use of steriods is a tendency to ulcerate or ulceration of lesions. Antibiotics should be used to prevent superposed secondary infection.

Splinting of paralysed limbs is necessary along with supportive treatment with vitamin and proteins.

In cases with extensive ulceration the patient should be treated on the lines of treatment for extensive burns i.e. covering the lesions with sterile dressing, adequate nutrition, proper nursing etc.

Thalidomide is of no value in borderline reaction (Sheskin, 1968). Clofazimine also has not been found to be of particular value. On the other hand, it has been found to aggravate the reacting condition in a case of borderline reaction till the patient chose to discontinue the treatment and got better.

Tuberculoid reaction

Though tuberculoid reaction is not a serious condition, a reaction of lesion over the face might cause a good deal of discomfort on account of the oedema leading to closure of eyelids. In some cases ulceration occurs. Severe painful neuritis of nerve in the region of the reacting lesions might result in paralysis. In tuberculoid reaction and reaction in borderline leprosy near the tuberculoid end, nonsteroid anti-inflammatory drugs eg. phenylbutazone and indocid are very beneficial when given in adequate doses. Injections of a vasodilator drug along with hydrocortisone, novocain and hyalase give gratifying results in severe painful neuritis; only rarely is systemic steroid therapy indicated. Nerve abcesses which form in the wake of tuberculoid or borderline tuberculoid reaction do not usually require drainage.

Antileprosy therapy in both borderline reaction as well as in tuberculoid reaction may be preferably begun with CIBA, 1906 or thiacetazone one tablet daily increased by one tablet fortnightly to 3 (i.e. 150 mg). When the signs of the reaction completely subside dapsone therapy can be commenced.

Treatment of intercurrent infection and attention to or elimination of any other provocative factor responsible for the reaction in the individual patient is called for. The dose of DDS should be individualised to the maximum which is tolerated by the patient. After a long reactionless period (eg. 1 year) the dose may be increased.

SUMMARY

1. The treatment of cases of mild and moderate intensity could be ambulatory, whereas cases of severe lepra and borderline reactions have to be hospitalised.

2. Reduction, temporary suspension or continuation of specific antileprosy treatment, likewise depends upon the severity of the reaction.

3. The basic antireaction therapy is either antimalarials or antimonials; cortiosteroid

therapy is indicated in life-threatening, potentially paralysing and blinding manifestations or where the basic therapy fails.

4. Thalidomide is very useful in steroid-dependent recurrent, sulphone intolerant patients, its use being confined to males.

5. Clofazimine is useful under the same conditions but the dose will have to be adjusted carefully, particularly in females.

6. Gradual induction of specific anti-leprosy therapy following the control of reaction and a gradual increase to adequate therapeutic dose is necessary.

7. Treatment for the relief of pain with analgesics and tranquilisers and reassurance for mental stress are part of the therapeutic regimen.

8. Careful nursing and maintenance of general health are called for. Investigation and elimination of the provocative factors in recurrent reactions help in reducing the frequency and severity of the reactions.

(The recommendation to reduce the dose, or withdraw DDS during reactional episodes as made in this article might have helped development of DDS resistance in *M. leprae* and is strongly opposed by clinical scientists as will have been evident from other articles in the volume. This is a serious dilemma for the field medical and paramedical workers who often don't have even the most basic reaction combating drugs at his disposal, and consequently is forced to suspend treatment to prevent further worsening of crippling neuritis, iridocyclitis, and such other complications. Obviously, only a full appreciation of this plight of, and sympathy for, the leprosy field workers on the part of the Governments can help the situation — *Editor.*)

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MULTIPLE DRUG THERAPY IN LEPROSY

A. B. A. KARAT

The introduction of Sulphones in the 1940's as specific antileprosy therapy brought in an era of euphoria coupled with uncritical enthusiasm for the prospect of curing, eradicating, controlling and preventing leprosy round the World. Certainly on the then available clinical and bacteriological data, this phase of optimism was probably justified since it came in the wake of the Chaulmoogra era, when despite prolonged continuous painful courses of injections of Chaulmoogra oil, one saw relentless progress of the disease in the majority of patients with multi-bacillary disease (borderline lepromatous and lepromatous leprosy) and the Clinician stood by the patient watching this steady deterioration in the patient's condition, finding himself therapeutically completely impotent to alter the course of the disease.

This was also the era when Penicillin superceded the sulphonamides with dramatic results in patients critically ill with bacterial infections. Whereas treatment with Penicillin was started with extremely small doses, e.g. 20,000 units 3-4 times a day, Sulphone treatment for leprosy was started with large doses (e.g. Promin). This accident in therapeutic adventure was to a large extent a fortunate one for patients with leprosy. Unlike the bacteria that were initially sensitive to extremely small doses of Penicillin and which later rapidly developed tolerance and resistance to Penicillin necessitating adminstration of millions of units of Penicillin today, *M. leprae* were exposed to very large doses of Sulphones (of the order of 1 G. a day) in the early days of Sulphone therapy—doses far in excess of the minimum inhibitory concentration of the drug against *M. leprae*. Even when Dapsone (D.D.S.) superceded the earlier Sulphones, patients were put on 600-700 mg. of Dapsone per week which provided at least 100-fold the minimum inhibitory plasma concentration of the active compound. It is this high dose therapy with Sulphones that delayed the emergence of resistant strains of *M. leprae*. It took 25 years of treatment with Sulphones before the resistant strains of *M. leprae* emerged. NO OTHER CURRENTLY KNOWN ANTIBACTERIAL AGENT HAS A COMPARABLE RECORD IN TERMS OF THERAPEUTIC EFFICACY.

The second major factor in delaying and minimising the emergence of Dapsone resistant *M. leprae* was the regular *daily* doses of Dapsone then in vogue. This daily dose regime maintained a fairly high and constant level of plasma dapsone throughout the period of treatment, further reducing the chances of development of drug resistance.

The introduction of "low-dose" Dapsone treatment in the 1960's following the observation that minimal inhibitory concentration of Sulphones in the mouse foot-pad system was only of the order of 0.003 μg/ml., led to widespread enthusiastic usage of low-dose Dapsone therapy for leprosy patients. It was also becoming obvious that in many centres, patients were given intermittent Dapsone therapy for leprosy, e.g. weekly and twice weekly doses since these were thought to be adequate to maintain plasma levels about the M.I.C. determined on the mouse foot-pad model. Another reason for interruption of Dapsone therapy was the belief that Dapsone itself was responsible for recurrent or chronic reactions in lepromatous leprosy and hence the logical therapeutic manoeuvre was to stop Dapsone till the reaction settled down—which took anything from two weeks to several months or years. Once the patient was free of reactions, it was recommended that Dapsone therapy be initiated cautiously with 1 to 5 mg. administered either daily or once a week. I myself have been guilty of this practice in the early sixties. There could be no more favourable clinical setting for the development of Dapsone resistance. It was further observed that after one to three years of fairly regular treatment, patient compliance for treatment

was falling off, especially in those with clinical regression of lesions.

One was also lulled into a false sense of security by the widespread acceptance of morphological index of the leprosy bacillus as an infallibly reliable indicator of the viability of *M. leprae*. In centres where progress of patients while on low-dose and intermittent Dapsone therapy regimes was monitored using morphological index (M.I.) as the main criterion of adequate control of disease, one failed to recognise the early phase of development of resistant strains of *M. leprae*. As far back as 1967, we drew attention to the fact that on 5 and 10 mg. of Dapsone a day, there was a perceptible rise in the total bacterial load as judged by bacterial index, often with concurrent clinical deterioration of the patient at about 30-36 months from initiation of treatment, though at this time there was no significant change in the morphological index of the bacilli which remained at zero. It is for this reason that the author abandoned further trials with low-dose Dapsone and intermittent Dapsone therapy nearly ten years ago. It appears to me that the clock has gone the full circle from the period when it was thought to be very scientific to treat multi-bacillary leprosy with homeopathically small doses of Dapsone, to the present view that such a policy leads to disastrous consequences in terms of emergence of bacterial resistance to Dapsone.

It is worth stating another obvious fact—there is no comparable bacterial disease in man to leprosy where there is such a vast abundance of organisms and massive bacterial load in the human body. Compared to this bacterial load in man, the bacterial load in the mouse foot-pad models pales to insignificance and, therefore, direct extrapolation of data regarding therapeutic efficacy of the so-called minimal inhibitory concentrations of Dapsone in the mouse foot-pad are not strictly applicable to the human. Similarly, the extrapolation of the significance of morphological index in the mouse foot-pad to the human situation is also equally fallacious. I have not been able to corroborate this alleged consistent relationship between M.I. and the viability of *M. leprae* in the human.

Thus the introduction of low-dose Dapsone therapy and intermittent treatment with Dapsone for any reason, were the major catastrophic trends that directly contributed to the upsurge of resistant strains of *M. leprae*.

Practically all the lepromatous leprosy patients reported to have developed secondary resistance to Dapsone—whether from Malaysia, Ethiopia, India or Carville—belong to the latter two therapeutic regimes. I AM UNAWARE OF A SINGLE WELL DOCUMENTED CASE OF RESISTANCE OF *M. LEPRAE* TO DAPSONE HAVING OCCURRED IN A PATIENT KNOWN TO HAVE BEEN ON REGULAR DAILY DOSES OF 100 mg. OF DAPSONE.

Therefore, the first requisite for effective treatment and control of leprosy is not the prescription of expensive polydrug therapy, but the re-introduction of "large" dose Dapsone daily, e.g. 100 mg. daily on a global scale. It should become malpractice for anyone to treat multi-bacillary leprosy with either intermittent or low-dose Dapsone. For this reason, Acedapsone must be withdrawn from the market before "epidemics" of resistant strains emerge. THERE IS AT PRESENT NO DRUG AGAINT *M. LEPRAE* THAT CAN CHALLENGE THE THERAPEUTIC SUPREMACY OF DAPSONE IN TERMS OF EFFECTIVENESS OF TREATMENT, LOW INCIDENCE OF SIDE EFFECTS AND LOW COST OF TREATMENT.

Whatever the reasons for the emergence of resistant strains of *M. leprae,* at present it is a fact that resistant strains of *M. leprae* are emerging at an ever increasing pace and pose a threat both to individual patient management and to epidemiological control of the disease. In this context, the comparison of *M. leprae* to *M. tuberculosis* is of limited value since the bacterial load in tuberculosis of any kind is relatively negligible compared to the bacterial load of *M. leprae* in multibacillary types of leprosy and because *M. tuberculosis* is rapidly killed and eliminated from the human body, normally between 12 and 24 weeks. However, the comparison is helpful between these two mycobacterial diseases in emphasising the need for and the advantages of multiple drug therapy in the control, cure, eradication and prevention of the disease.

The most important aspect of using multiple drug therapy with striking advantage, is in the reduction of the incidence of emergence of drug resistant bacilli directly attributable to the therapeutic policy of monotherapy to

insignificant proportions. The efficacy of such combined treatment is based on firm bacteriological considerations and is extremely relevant to the development of a therapeutic policy in the management of leprosy.

On general principles, it is obvious that drug resistance tends to result from the presence of a very small proportion of organisms in a given bacterial population that are resistant to a given drug and with the passage of time, these multiply sufficiently to re-populate the patient entirely with the resistant strain. This very small proportion of resistant organisms hardly ever exceeds 1 in a million (10^{-6}). It would appear, therefore, that one would need to ensure that not only is one giving more than one specific drug, each with differing mode of action against the organism, but also that one has adequate concentrations of each drug in the tissue to be active against the micro-organism.

It is also imperative that the choice of the combination of multiple drugs must recognise the existence of cross resistance between drugs of similar chemical structure and mode of action and, therefore, avoid combinations which are likely to result in the emergence of resistant strains more quickly and easily. The available antileprosy drugs of proven value could be grouped as follows, and it is suggested that only one drug from each group should be used in any combined drug therapy regime:—

1. **Sulphones:**

   Dapsone

   Acedapsone

   Long-acting sulphonamides (Fanasil, Lederkyn, etc.).

2. **Thioureas:**

   Thiambutazone (Ciba 1906)

   Thiacetazone (Thiosemicarbazone, TB_1)

3. Rifampicin.

4. Clofazimine (B663)

5. Streptomycin

6. Isonicotinic Acid Hydrazide (INAH)

7. ? Chaulmoogra.

Before discussing possible combination of drugs, it may not be out of place to elaborate the economics of polytherapy in leprosy since the vast majority of sufferers from leprosy live in poorer countries with limited financial resources for health care. Under such circumstances, practical considerations of financial outlay must be balanced with the ideal therapeutic policy based purely on theoretical considerations of bacteriological, therapeutic and epidemiological significance. It must be mentioned at the very outset, therefore, that the two main recent introductions to the therapeutic armamentarium against leprosy, namely Rifampicin and Clofazimine, are both expensive drugs and, therefore, beyond the reach of 99% of leprosy patients. Clofazimine unfortunately has the additional disadvantage of producing a striking discolouration of the patient's skin following exposure to treatment for more than a few days. These two drugs may, therefore, have a particular place in the overall management of patients with leprosy under very special circumstances. It is also worth noting that, in countries like India, where a significant proportion of patients with multi-bacillary types of leprosy also have concurrently *M. tuberculosis* infection, Thiacetazone and I.N.A.H. have long been used concurrently with Dapsone with significant improvement in both tuberculosis and leprosy. Since many thousands of such patients have already been exposed to this combination of drugs, which incidentally is perhaps the most inexpensive combination currently available for management of leprosy, it would seem logical to suggest this as the first line of combination therapy in leprosy. One or two hazards may be mentioned in passing. First the occurrence of exfoliative dermatitis in patients exposed to Thiosemicarbazone (Thiacetazone) and of peripheral neuropathy in patients on I.N.A.H. Both these complications, as a rule, tend to appear during the first 12 weeks of treatment and it is, therefore, essential that patients started on this combination of drugs are screened frequently during the first 12 weeks of treatment and given specific instructions to stop the drugs straightaway at the first appearance of symptoms of these complications and to report to the base hospital for further treatment.

The following permutations and combinations of drugs are suggested based on theoretical considerations. None of these regimens have been subjected to long-term trial in lepromatous leprosy.

1.	Dapsone 100 mg. —	in a single daily dose for at least five years or until
	Thiacetazone 150 mg. —	such time as the patient becomes bacteriologically
	I.N.A.H. 300 mg. —	negative on three consecutive monthly examinations and then to follow with :—
	Dapsone 50 mg. —	daily indefinitely, (certainly for a period of not less
	Thiacetazone 150 mg. —	than 20 years). It is imperative that all drugs must be administered together every day.
2.	Dapsone 100 mg. —	daily. Again, the two drugs to be given together
	Thiambutazone 1 Gm. (Ciba 1906) —	in a single dose.
3.	Dapsone 100 mg. —	
	Thiambutazone 1 Gm. —	daily in a single dose.
	I.N.A.H. 300 mg. —	
4.	Dapsone 100 mg. —	
	I.N.A.H. 300 mg. —	
	I.M. injection of —	daily for 60-90 days.
	Streptomycin 1 Gm. —	
		To be followed by :—
	Dapsone 100 mg. —	daily until the skin smear is negative on three conse-
	Thiacetazone 150 mg. —	cutive occasions when the Dapsone could be reduced
	I.N.A.H. 300 mg. —	to 50 mg. daily, Thiacetazone 150 mg. daily. The
	—	I.N.A.H. could perhaps be discontinued at this stage.
		This regime is specially useful in lepromatous leprosy complicated by tuberculosis, severe nasal, laryngeal involvement in lepromatous leprosy as well as in nodular and ulcerated, highly positive lepromatous leprosy.
5.	Dapsone 100 mg. —	
	Clofazimine 100 mg. —	daily for one year.
		Followed by :—
	Dapsone 100 mg. —	
	Thiacetazone 150 mg. —	daily indefinitely.
6.	Rifampicin 600 mg. —	
	Dapsone 100 mg. —	daily for one year.
		Followed by :—
	Dapsone 100 mg. —	daily until the patient is bacteriologically negative on
	I.N.A.H. 300 mg. —	three consecutive occasions and maintained on Dap-
	Thiambutazone 1 Gm. —	sone 50 mg. daily, Thiambutazone 1 G. daily.
		For reasons already explained, intermittent regimens with Rifampicin should be discouraged despite financial considerations.
7.	Rifampicin 600 mg. —	daily, until the patient is bacteriologically negative
	Clofazimine 100 mg. —	and maintain on :—
	Dapsone 50 mg. —	

Dapsone 50 mg. —
Clofazimine 100 mg. — daily indefinitely.

8. Long-acting Sulphonamide 1 Gm. — daily.

9. Long-acting Sulphonamide 1 Gm. —
Clofazimine 100 mg. — daily for one year.

Followed by :—

Long-acting Sulphonamide 1 Gm. —
Thiambutazone 1 Gm. — daily indefinitely.

It is thus apparent that one has a wide choice of therapeutic regimes available and the choice may be primarily dependent on the economic situation of the particular patient. There is advantage in choosing combinations that contain Clofazimine for treatment of patients with a tendency to reactions since suppression of reactions appears to be one of the most outstanding advantages of Clofazamine treatment. By the same token patients with a tendency for recurrent acute neuritis may be better treated with combinations containing long-acting Sulphonamides or Clofazimine since both seem effective in controlling these acute episodes of neuritis. It may also be worth adding Pyridoxin 10 mg. daily for all therapeutic regimens that contain I.N.A.H. This would markedly reduce the chances of the development of peripheral neuropathy in such patients as a side-effect of I.N.A.H.

SUMMARY :

The most effective measure against widesspread emergence of Dapsone resistant *M. Leprae* is the regular daily administration of "large doses" of Dapsone (e.g. 50 to 100 mg.) orally. It is also the most economic way of controlling leprosy. In the highly bacillated types of leprosy, multiple drug therapy will further reduce the incidence of occurrence of resistant strains of *M. Leprae*. Whatever polytherapy is adopted, it is essential to ensure that firstly one is using combination of drugs that has different chemical structure and pharmacological action. Secondly, the individual drugs must be used in adequate daily dosage and intermittent treatment must be avoided at all costs.

On economic grounds and ease of administration, wherever practicable Dapsone 50 to 100 mg. daily, Thiacetazone (Thiosemicarbazone) 150 mg. daily and I.N.A.H. 300 mg. daily is probably the best combination, along with Pyridoxin 10 mg. t.d.s. In highly bacillated patients with nasal and/or laryngeal involvement, combination of Dapsone 100 mg. daily with I.N.A.H. 300 mg. and I.M. Streptomycin 1.0 Gm. daily for 4 to 12 weeks is recommended. If money is no object, such patients could be treated equally well with combination of Dapsone and Rifampicin. In patients at risk with recurrent/chronic lepra reaction, combination of Dapsone with Clofazimine is probably the first choice.

ROLE OF PHYSIOTHERAPY IN THE TREATMENT OF LEPROSY

A. J. SELVAPANDIAN

Effective application of newer methods of physical medicine comprising all the component disciplines of rehabilitation has opened the way to a fuller life for the leprosy patients.

The skills of the rehabilitation team—consisting of the surgeons, nurses, physical therapists, occupational therapists, social workers, para-medical workers and other trained personnel are integrated as a single force to assist the leprosy patient to reach his physical, emotional, social and vocational potentials to the maximum.

For the effective implementation of all the various disciplines of rehabilitation, facilities and personnel should be available without much difficulty. Very often even the uncomplicated cases receiving medical treatment will need advice and other treatment from one or more of the rehabilitation team.

Deformity in leprosy is considered to be the main obstacle in the total rehabilitation of the leprosy patients. The numerous complications which occur in the extremities and occasionally in the face and in the eyes as ulcerations, gross destruction of bone and joint and loss of limbs are preventable, if adequate early measures are undertaken. The immense value of preventing such complications with simple measures is now well recognized. The paralysis of the peripheral nerves gives rise to loss of motor, sensory and vasomotor functions. Though the motor loss is compensated by muscle balance surgical operations, the residual loss of sensory and vasomotor functions has been responsible for most of the disabilities and complications.

Among the available aids of physical medicine, Diathermy is of value in neuritis and Electrotherapy in muscle stimulation. These are of limited value and therefore need not be an essential part of a physiotherapy unit. Massage and exercise are important. Splinting should be recognized as fundamental for immobilizing inflamed nerve and infected hand.

The effective application of the various procedures of physical medicine is the concern of the physical therapist, occupational therapist and the person in-charge of the prosthetic and orthotic service. And, they should always work in a co-ordinated manner. The application of these methods would vary in the mode, intensity and frequency of application depending upon the stage of the disease, and the particular problem. Deformities would fall under the following categories:

1. Preventable deformities
2. Early deformities
3. Fixed deformities.

PREVENTABLE DEFORMITIES

Properly supervised medical treatment is necessary in all cases. Anaesthesia of the extremities, even in the absence of deformities, should be taken care of at this stage, which would prevent the onset of ulcers, deformities and disabilities. These patients should be instructed to wear simple foot-wear with microcellular in-sole at all times, and suitable instruction given in the case of the hands and feet in preventing ulcerations, burns and blisters and, in the event of any of these things occurring, the need for immediate and proper treatment. Frequently, the dry skin predisposes to ready ulceration and this is best prevented by simple measures like soaking the limb in water follwed by application of oil. If fact, the lack of moisture in the skin is responsible for the breaking up of the skin, and the oil application over moist skin helps to keep the moisture in. Daily inspection of hands and feet for evidence of blisters, aberrations, foreign bodies like thorns

could be taken care of then and there without allowing this to progress into something serious like an infection or deep-seated ulcer. If a particular occupation or activity has brought on such injuries possible adapation of tools or modification of equipment should be provided with the advice and help of the occupational therapist. The prosthetist could provide the patient with the necessary foot-wear or fit the tools used by the patient with the necessary adaptations. Most of these implements in the case of the gardener, carpenter or even the house-wife would require simple devices and adaptations, which would protect the hand from injuries, burns or blisters.

Cases of early paralysis need attention and care in preventing the development of total paralysis and progressive deformities. Simple splints made of plaster of paris would meet, by and large most of the requirements. Proper care must be taken to see that splints are well padded, especially against the bony prominences, to prevent the occurrence of pressure sores. Regular exercises, done under the supervision of the physiotherapist, would keep the joints mobile, and the skin supple. Progressive resistance-exercises could be taught in cases of incomplete paralysis when satisfactory recovery of function may result. The occupational therapist would be able to guide the patient in the suitable occupation with modified tools which would enable the person to pursue his occupation without the risk of injury to the hands and feet.

EARLY DEFORMITIES

The majority of deformities are due to complete nerve paralysis resulting in claw hand, foot-drop and lagophthalmos. The muscle imbalance which is the result of paralysis throws these joints in extreme positions resulting in contractures and fixed deformities. The physiotherapist uses all the methods of physical medicine to keep the joints mobile with assisted active exercises, passive exercises, lively splints and special splints. Simple splints should be provided to prevent any further contracture. The patient is taught the use of oil massage and assisted active exercises which should be carried out at home if he is waiting for reconstructive surgery or any special brace. The appliances and splints for use in such conditions should be simple, easily available, and acceptable to the patients. They are very important in keeping the limb in the functional position and even allow the patient to carry on his normal activties suitably guided by the occupational therapist.

In appropriate cases, the static or the dynamic splint could be provided. The latter supports the involved part in a functional position and provides a range of activity for the uninvolved muscles of the part. The static type of splint on the other hand holds the involved part in a functional rigid position for a specific period if there is any need for the inflammatory process to subside.

FIXED DEFORMITIES

These usually involve the joints which are not treated in the early stages resulting in contracture of the skin, the soft tissue, occasionally tendons and capsule of the joint. Infrequently, the joint may be subluxated with disorganization of the joint. Deformities due to "reaction" are most difficult to correct as the fibrosis and the contracture involved all the tissues and they are by far most resistant to any form of treatment.

Deep-seated infection involving the skin, tendon and bone and joints would result in serious fixed deformities. Such cases are the least likely to be helped by any form of physical therapy.

Neuropathic changes occurring in the foot with disorganisation of the joints should be recognized early and the harmful nature of continued walking on such feet should be recognised. Use of crutches or walking-plasters and in special cases non-weight-bearing prosthetic devices should be adapted.

A qualified and trained physiotherapist or technician determines the success of cases which undergo reconstructive surgery. In the first place, the hand or the foot must be in an ideal condition before operation, i.e. without any contracture and the muscles in peak condition. From the point of post-operative re-education, the patient must be taught how to contract a muscle or a particular group of muscles. Prompt treatment of post-operative oedema and stiffness with appropriate measures, and use of splints and re-education exercises will require all aids of physical medicine to be brought into use with skill and discretion on the part of the physiotherapist.

Occupational therapy is not only an aid to the surgeon, but supplements physiotherapy

treatment in the preoperative and post-operative care of patients. The function of occupational therapy is to restore physical function, to increase joint motion, muscle strength and co-ordination.

To meet the needs of the leprosy patients comprehensively, it would be ideal to have a physiotherapist, an occupational therapist, a social worker and an orthotic technician, supervised by the medical officer, well-oriented in leprosy rehabilitation. In many leprosy centres, the idea of comprehensive care of the leprosy patient leading to total rehabilitation is steadily being recognized and appreciated. Asylums and sanatoria are progressively becoming treatment centres, and increasing numbers of patients are now being discharged than ever before. Every one of the medical officers should recognise the new concept of the care of leprosy patients. Orientation and refresher courses on leprosy in all its aspects should be conducted at the main teaching centres for the medical officers. This will enable the doctors to better appreciate the need for setting up the various aids of physical medicine in their respective centres. Thus, he will be able to supervise and co-ordinate the activities of all the technicians.

Qualified and trained personnel like physio-therapist, occupational therapists, social workers and orthotic technicians, having had special training in leprosy are not easily available at the present moment to meet the needs of the existing training and teaching centres. The paucity of trained personnel and lack of funds are the main reasons for the non-availability of such facilities in most of the centres. At best, now, there may be a para-medical worker, or a welfare worker who might be responsible for the distribution of tablets and related work.

The vital role played by the para-medical field worker in the control programme centres is that he contacts the patient even in remote areas, and thus plays an important part with regard to the preventive aspects of deformities, if equipped with adequate knowledge of principles of physiotherapy and early treatment of ulcers, in addition to his other duties. It should be possible to include, during the training of a para-medical worker, practical methods of management of deformities and plantar ulcers. He should also have a part in the education of the patients. It should be stressed that prevention of deformity and encouragement of manual activity and skill among the patients should be his additional responsibility.

The employment of a qualified physiotherapist is perhaps not necessary in small centres as the practical methods of management of deformities is well-known to a properly trained physiotherapy technician. The needs of many centres are now met by the ready availability of well-trained physiotherapy technicians who have a good knowledge of the principles of management of deformities, their prevention, care of the anaesthetic extremities, and practical experience in all the aids of physical medicine. Such technicians have undergone training in recognised teaching institutions, with qualified and experienced staff, managing a busy physiotherapy department attached to the reconstructive surgery unit. The technicians get additional experience in the pre-operative and post-operative management of surgical cases also. Active participation in the ulcer clinics affords them the experience of the treatment of ulcers and the fitting of the appropriate foot-wear.

The prosthetic technician who supervises the making of the special foot-wear and appliances, including crutches, can be made responsible for training a cobbler (Very often an ex-patient is too happy to undergo this training and thus return to his centre as a useful member of the team. We have four cobblers in training at a time). The technician, in addition to his practical training, should participate in the programme of teaching and propaganda to help patients to learn a way of life whereby the risk of damage to their hands and feet may be minimised. The additional knowledge in occupational therapy methods would be of great value in giving the patients the appropriate tool adaptations and advice, so that they can continue to occupy themselves usefully, but without damaging their hands and feet.

Of course, the therapist should always refer to the medical officer, whenever possible, all cases of deformities and ulcers, and work under his instructions. An enthusiastic physitherapist or technician should not limit his work to the confines of the institutions, but extend it to the village control centres where advice and help may be given to patients receiving out-patient treatment and also to patients making adjustments to life at home.

SPECIAL ROLE IN A CONTROL UNIT

Effective leprosy control programme should be able to detect early and treat adequately every person suffering from leprosy. In

such an ideal situation, there may not be any need for rehabilitation measures including surgical treatment. Such a person will not become deformed since nerve damage is prevented, he will not become psychologically affected since the environment will not necessarily induce such an attitude, and he will not be socially dislocated since he continues to live in the community as a member of the family and for this reason he will not be economically affected. However, such an ideal situation with adequate treatment following early diagnosis is not always attained.

At the field clinics, the assessment of deformities should be done ideally by a physiotherapy technician. In practice this may not be possible as the para-medical worker is the person who is in contact with the patient and therefore he must be in a position to do a preliminary assessment. He must be also in a position to carry out simple home treatment measures like oil massage, assisted active exercises, P.O.P. application and give suitable advice.

MANAGEMENT OF NEURITIS

For early nerve inolvement, provide P O P slab to rest the limb in the functional position or sling, and other devices for elevation of limbs in case of acute swelling. Such of those cases which need to be re-examined by the physiotherapy technician and the medical officer for final disposition may be referred to the regional centre.

To enable the para-medical worker to be more precise in the detection and preliminary treatment of very early deformities and other related surgical conditions greater stress be laid on the teaching of physiotherapy in the training of the leprosy-para-medical workers. Neuritis of a single nerve following assessment of its function could be treated at the home of the patient by providing support for rest and immobilization. P O P padded slab will be ideal which would mean that the necessary materials are available and the worker had experience in applying this support with sling or simple splint for the upper limb will be alternate methods.

MANAGEMENT OF EYE

The instructions and training given to the worker should emphasise the recognition of common eye complications in leprosy, in the field.

Routine and careful examination of the eyes for evidence of conjunctivitis, corneal ulcers, and iridocyclitis should be done on all patients. Any undue delay in the treatment may lead to serious complications resulting in loss of eye-sight. Provisions should be made for the doctor to see such cases and advise hospitalization for special care. Use of eye shades, sun glasses, eye drops of atropine, antibiotics or eye ointment will prevent further damage and these should be made available.

The early cases of lagophthalmos can be treated with home physiotherapy measures like active exercises and gentle massage which are helpful in the recovery and prevention of further deterioration. Established cases should be operated upon as early as possible. Medial and lateral tarsorraphy are procedures easy to perform compared to temporalis transfer.

MANAGEMENT OF NOSE

Unfortunately very little attention had been paid to conditions of nose. Accumulation of discharge and crusts in the case of infection of ulcerated nasal mucosa can be a very distressing symptom and this discharge is a store-house of the bacilli, in the infectious cases. Routine saline, irrigation and instillation of nasal drops by the patient himself will be a good practice which will reduce the danger of contamination as well as afford comfort to the patients.

MANAGEMENT OF CASES IN REACTION

The acute phases termed "reaction" particularly in the lepromatous and border-line cases give rise to some of the severe deformities with permanent disabilities. The hand is particularly involved with severe swelling, pain and muscle spasm due to involvement of all the tissues. Splinting to the hand in the functional position, local heat, elevation of the limb and absolute rest are of immense value in preventing the onset of serious deformities. The physiotherapist has the great responsibility of immobilising the joints in the functional position, and judiciously mobilising the joints by gentle exercises. Gentle movement of the digits should be steadily increased as the swelling and pain begin to subside.

Cases with acute neuritis are benefitted with application of local heat, and splinting

of the limb concerned till the symptoms settle down. In such instances with careful supervision and painstaking treatment on the part of the physiotherapist, occupational therapist and the nurses, surprisingly good results could be achieved. Occasionally, the major joints, like knee and ankle, may be the site of deformities, due to uncontrolled muscle spasm, resulting in contractures. If timely interference and appropriate physiotherapy treatment is not instituted these joints could become very stiff and subsequent physiotherapy treatment would be of little value.

A centre with an experienced surgeon, a physiotherapy unit and an operation theatre serves a very important function in providing facilities for reconstructive surgery. As more surgeons become available many centres will be able to take care of a larger number of cases who will be benefitted by surgical procedures. A regional centre tends to be crowded with patients waiting for operations. At the same time, the time and expense involved in travel and waiting and for physiotherapy are beyond the means of an average patient.

Regular visits to the peripheral clinic by a mobile team of surgeon, technician and asssistants with equipment will enable the team to suitably advise the treatment for problem cases, operate on cases which are already pre-selected and prepared by the technician, and review post-operative cases which were operated on previous visits. Such a visit at regular intervals covering several centres will help a large number of patients who are in need of advice, surgical treatment and reconstructive surgery. Any problem cases can be moved to regional centres.

Of course each of these centres should have a trained physiotherapy technician and facilities for surgery. It was found that in spite of some of the disadvantages, such a programme of mobile clinics have met the needs of those who could not afford to go to a recognised regional centre for such treatment.

Again it must be emphasised that the main purpose of such visits should be to supervise and advise on the prevention and treatment of early deformities and ulcers and develop a programme of teaching and publicity to help patients with anaesthetic extremities to learn a way of life with minimal risk of damage to their hands and feet. Advice on adaptation of tools and implements and suitable protective foot-wear would also form part of the programme.

CONCLUSION

The great strides made in the field of physical medicine have, when properly utilised, proved to be a great boon in the rehabilitation of a leprosy patient, with or without deformities. For the success of any leprosy treatment centre the work of the entire team consisting of a surgeon, physiotherapist, occupational therapist, prosthetician and para-medical field-workers should be co-ordinated and correlated.

The establishment of regional centres with the full complement of personnel and facilities and field centres with basic personnel and facilities would go a long way in promptly attending to the medical and rehabilitative needs of patients most of whom live in rural areas.

THE SCOPE OF CORRECTIVE SURGERY IN LEPROSY

Ernest P. Fritschi

Deformity in leprosy is of two main types. The first is that which occurs during the activity of the disease, and is directly attributable to the disease process. This is called Primary Deformity.

Secondary Deformity on the other hand, may occur at any time after the disease is completely cured and when there is no more active disease process going on. It is commonly the result of injury occurring to the fingers and feet which have lost sensation and hence have no protective defence against harmful external forces. These injuries frequently become infected with pus-producing organisms which, because the patient does not look after his finger (since it gives him no pain), then penetrates deep and affects the bone. The infected bone, usually that of the finger tip then dies and is extruded, resulting in the shortening of the finger. More virulent infections can result in the loss of more than one bone and even in permanent stiffness of the whole hand and occasionally gangrene. All this damage is caused not by the leprosy organisms but by various pus-producing organisms common to anyone.

There is very little that Surgery can offer in the correction of secondary deformity. If an infection is seen early enough, it can be treated surgically by splinting, drainage and antibiotics and the course of the infection can thereby be limited, but once a bone is lost there is no satisfactory way to restore finger length. The surgeon in these cases must take steps to teach the cured patient how he should look after his fingers and feet which have no protective feeling of pain. This means intensive teaching in the care of hands and feet (Fig. 1)

The nature of the problem

Primary deformity is the field in which there is a very real place for corrective surgery. The commonest cause of primary deformity is a paralysis of one or more of the mixed nerve trunks of the extremity. In leprosy these nerve lesions occur at certain well established sites and the consequent loss of muscle power also falls into a definite pattern.

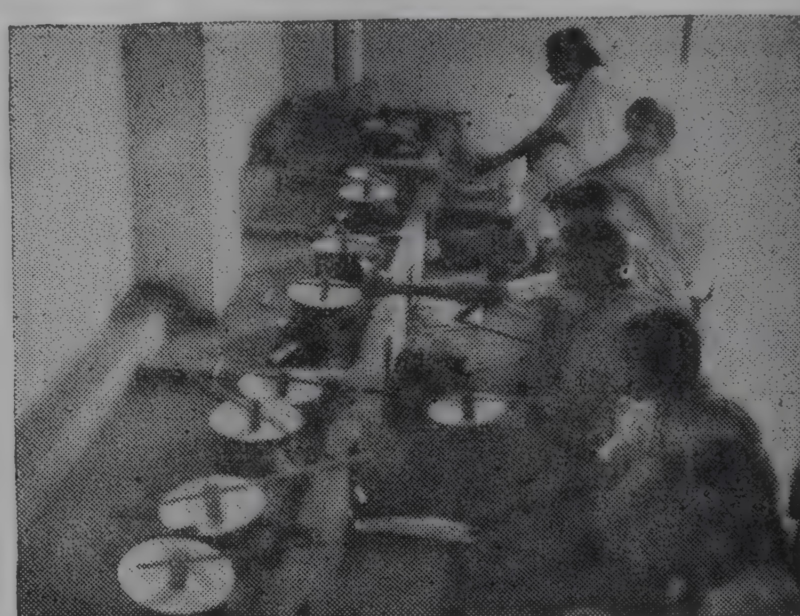

Fig. 1 Prevention of secondary deformity: Cooking class in progress with safety gadgets in use.

The consequence of paralysis is two fold, namely, a loss of the normal graceful appearance of the fingers, and loss of function. It is usually taught that the latter is more important and appearance is secondary. This view point is natural since the hand is generally considered to be the instrument by which man is able to work. In leprosy however, another factor is powerfully at work and that is the factor of the community.

In all countries where leprosy is prevalent it is feared. This fear seems to be based on the deformities which it sometimes gives rise to. These deformities are well known and when recognised, result in the social ostracisim of the patient and his loss of employment. The appearance of the hand must therefore have a particular importance which is not so evident in other hand injuries. When given the choice between appearance and function the patient often chooses appearance. The surgeon who is new to leprosy, sometimes does not fully appreciate this and tends to

think that the patient is over preoccupied by "cosmetic" considerations. This is not so. The patient realises from his experience that he can learn to accomplish most activities, even with hands that are partially disabled, but he has no defence against an appearance which the public will not accept. He cannot hide his hand or his face, and these deformities cost him his job and his place in society, of what use then are hands which might be a shade more functionally efficient if the owner is not given the opportunity to use them?

In leprosy therefore, the appearance of the hand is as important a factor to be considered as is the function.

The size of the problem

It is generally recognised that about 20-25% of all leprosy patients suffer from some deformity of the hand or foot or face. There are estimated to be about 3 million leprosy patients in India today. This means that there are approximately 6 lakhs (6000,000) patients in India who have visible deformity. Most of these patients cannot benefit to any worthwhile extent by corrective surgery. There are no figures available to indicate the proportion who have correctible deformity because the opinions of surgeons as to what is correctible must necessarily differ.

However, even supposing that only 10% of this deformity is correctible, the figure is formidable considering that the average full time surgical unit only carries out an average of 350-400 operations per year involving perhaps 250-300 patients.

It is probably true to say that in areas where the leprosy control programme has been working with a reasonable degree of effectiveness the developing of new deformity is less common. Neuritis is beginning to be recognised early enough for atleast a proportion of the cases to be saved from irreversible paralysis. But even in the best run areas there are still cases which inevitably go on to paralysis. This situation is likely to continue for some more years until the early enlightened treatment of leprosy becomes the rule instead of the exception. It may therefore be assumed for all practical purposes that about 10% of all new cases occurring in India today are still likely to develop nerve trunk damage. Perhaps half of these may be prevented from paralysis by early effective treatment. Assuming this, and assuming also that the present incidence rate of new cases per annum in the whole country is around 0.2 per mille then we can anticipate roughly 0.04 per mille new cases of paralysis per annum or a little over 2,400 per year. Enough work for five full time surgical units. This is of course a very rough estimate based on extrapolation from figures which apply to the more endemic areas but which are corrected so that they can reasonably be considered valid for the whole country.

Thus, although there is no doubt that with the increasing availability of early treatment the incidence of deformity can be expected to come down, there seems to be no justification for the belief that there is not likely to be any work for the reconstructive surgeon within the next few years. Unless, as in Polio, an efficient vaccine is soon discovered there is little hope of this optimistic situation.

What can surgery achieve?

Alistair Maclean[1], in a popular work of fiction puts the following remark into the mouth of one of his characters: "Plastic surgery can be very long, very painful, very expensive and occasionally not very successful." With the possible exception of the second adjective, all this could be said of corrective surgery in leprosy with equal validity.

The first question that the surgeon has to ask is whether anything can be done for a particular patient? This may sound common place, but the field of leprosy is littered with patients who went to a surgeon with a particular set of deformities and left him several months, sometimes years, later with another set of deformities! Changed? Yes, perhaps 'improved' technically, but in practice in the same position of being unable to get a job.

For nearly every single deformity there is an operative answer to correct the deformity. But this process can be carried to the point of becoming ridiculous. The decision is not therefore purely surgical, but it involves the whole team of surgeon, social worker, physiotherapist and occupational therapist. The background, age, previous employment, social status and likely future employment must all be taken into consideration. It is important to emphasise that it is the whole patient which is being treated and not merely the hand or foot or face.

The second question to be asked is, what should be done?

Here there are two principles which should guide the team in making the decision, namely, function and appearance. In most centres of reconstructive surgery in the world the former consideration far outweighs the latter. It is assumed that the hand is purely a functional organ that requires to be restored so that grasp and pinch is possible. In fact there is no functional position applicable to all hands. A carpenter and a farm labourer require fingers in both hands which can close around a cylindrical object with a diameter of about 3-5 cm. and hold it firmly. A desk worker, teacher, etc. require a right hand which can hold a pen or chalk in a secure three finger pinch. Various other occupations require their own particular activities and it is essential for these activities to be clearly understood.

Essentially, reconstructive surgery makes use of one or more healthy muscles whose action is relatively not so important, to replace the action of other paralysed muscles which are more essential. The ultimate use of the transferred muscle to achieve the desired function is a trick that the patient must learn, and having learnt it, must apply unconsciously while doing his work. The older the patient, or the less his understanding of the function of the muscles and tendons, the more difficult he will find this process of re-education and the more imperfect will be the result.

There are therefore cèrtain factors to be taken into consideration before operating.

a. Age of the patient

The younger the patient the better the final result both in appearance and in function. This is because he can easily learn the new trick, and it can become part of his activities until its use is completely unconscious. The older one gets the more difficult is this process. It is therefore very rewarding to operate on children and the results are more encouraging (Fig. 2). It may in fact be said that there is no lower age limit to reconstructive operations in children. The youngest we have operated was about 6 years old, with an excellent result.

b. The timing of the operation in relation to the onset of paralysis

The longer the time interval, the more difficult he finds it when he has to learn a new pattern. There is also the danger of the fingers getting damaged, and the joints becoming stiff. It is difficult for the patient to remember to do his exercises regularly sometimes for years, before he is considered to be safe for operation. Timing has also to be considered in relation to the disease and its treatment.

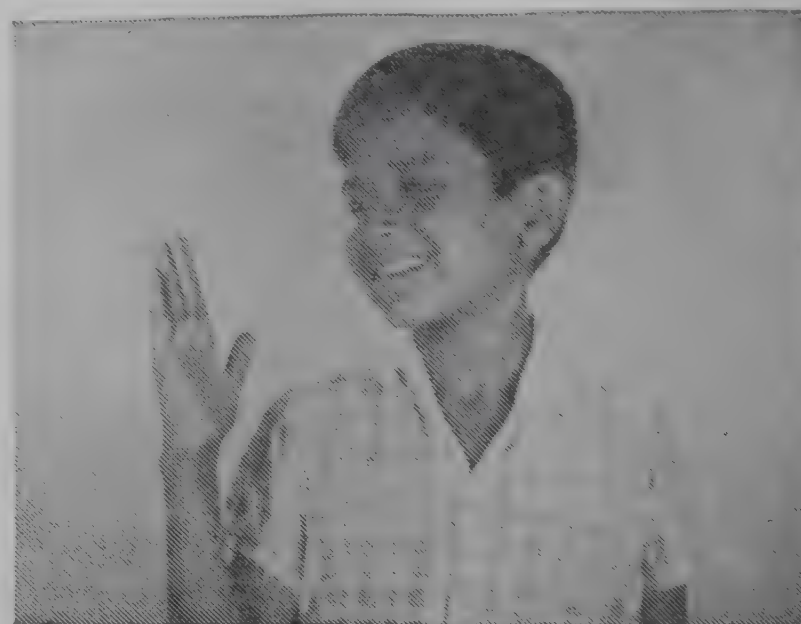

Fig 2 A happy young patient with his newly operated hand.

It is emphatically stated that in our experience it is not necessary, and in fact not at all desirable, to wait for a patient to become completely inactive before operating. This process is too long drawn out and his dehabilitation is therefore too far advanced by the time he gets 'ready for surgery', hence rehabilitation often becomes impossible. The risk of 'reaction' or exacerbation of the the disease[2] is very small and, should it occur, it can be easily and effectively dealt with since the patient is right under our observation.

A safe rule is to establish the patient on treatment with full doses of D.D.S. for a period of about three months before operation. This time can be profitably used to teach the patient the care of his hands and feet, and to isolate the action of the muscle which it is intended should be used for the reconstructive operation.

One objection to early operation which is sometimes raised, is that other nerves may subsequently become paralysed. This may well be, although paralysis tends to occur at the time of the turning point in the patients immune response to the organisms, and as such is often a single period in the natural history of the disease. If however, a further episode does take place there is still no reason why it cannot be dealt with by another operation. It is very exceptional for a radial nerve paralysis to develop, thereby rendering func-

tionless a previously active extensor muscle which has been used for a transfer.

c. The state of the hand

The hand should have mobile and undamaged finger joints. Long standing paralysis tends to adapt both the skin and the underlying dorsal expansion over the proximal finger joint to the flexed position, so that when the finger is extended, a pad of skin lifts up over the back of the joint. These 'kunckle pads' are the external signs which indicate an alteration in the mechanics of the joint and which therefore point to a bad prognosis. Damage may also have occurred to the joint itself usually by neglected injury over the permanently flexed kunckle. Such damage often renders a tendon transplant useless and the finger joint has then to be permanently fixed in a better position. Finally loss of finger length is also a consideration. The best functional result is often rendered poor because of the ugliness of shortened stubby fingers.

d. The nature of the patient's employment

This is probably the single most important factor in the long term prognosis of the surgically corrected hand. Follow up studies indicate very clearly that where a person has a supervisory job, or one which is clerical and non traumatic to the hands, the operated hands will continue to be in good condition for many years. But in the case of manual workers whose hands are constantly subjected to severe trauma such as farm labourers etc. the hands, though often still giving indications that the operations had been successful, in many cases are shortened, scarred and often very seriously mutilated.

This observation emphasises the need for very intensive teaching in the care of hands and feet in such persons. In such persons with heavy manual work there may still be a place for surgery so as to expose the proximal segments to the tool and not, as in the case of the claw hand the tips of the fingers. But any procedure that is done must be accompanied by practical training in the careful use of his hand.

In the case of desk workers the type of operation required is one which gives a good right hand pinch and a good cosmetic result. Such persons have to expose their hands to the public and it is essential that they look as normal as possible. In patients whose fingers are very severely clawed with joint damage, arthrodesis or joint fixation can be considered. If this is done the fingers become stable and good-looking provided the angle of fixation of the P.I.P. joints is minimum and graded from index to little, so as to look as natural as possible. Arthrodesis of the finger joints is also useful for eating with the hands and this activity involves fingers which need not be flexed.

When a patient has a triple nerve paralysis, i.e. a claw hand, a paralysed thumb and a wrist drop, the hand is indeed about as useless as it can be. It can never be reconstructed to serve with any power, but it can be well repaired for a person whose work requires only light use. Here again arthrodesis is a good procedure but attention should be given, not to function but to appearance in the selection of the angle of fusion.

In brief, persons who are self employed must have hands that are first of all functional and secondarily cosmetically acceptable if they are to retain their jobs. It remains a remarkable truth that the human being can learn to adapt and utilise remaining abilities to an astonishing extent and even unfunctional hands can perform most required activities.

e. The social status of the patient

Here again the appearance of the hand must take supremacy over the function. The greatest difficulty of persons in the upper social level is to move freely with their associates. It is important to supplement any corrective surgical procedures with psychotherapy to improve the persons self confidence.

The reconstruction of the hand

There are two main patterns into which the upper limb paralyses fall, the 'claw hand' and the 'ape thumb'. Subject to the consideration of indications and contra-indications as outlined above, both these deformities can be corrected with good results.

The claw hand is the result of the paralysis of ulnar nerve which supplies the small muscles of the hand and controls the mechanism of the extension of the finger joints. There are fourteen such muscles in the hand, and they are responsible for cupping of the palm, finger extension and the ability to approximate the finger tips and to splay out the fingers. The strength of the grip is the responsibility of the large forearm muscles. The small intrinsic muscles of the hand only control position and finer movements.

Obviously it is not possible to find 14 healthy muscles to replace these paralysed ones. Therefore it is not possible to restore all the actions and the surgeon must decide which are the most essential ones.

It is generally accepted that one of the essential actions is to flex the fingers at the point where they meet the palm, and to hold the finger joints themselves firm in an almost extended position while this is being done. This is the movement required for holding objects, for eating with the hands and for picking up things against the opposed thumb. This position has been called the intrinsic position since it is the position resulting from the use of the intrinsic muscles of the hand. To do this several operations have been designed and are in common use. The indications for their use are fairly clear and generally accepted. They fall into two main groups: those which utilise one of the long muscles of the forearm which is lengthened by a free grafted tendon, which is divided into four tails one of which goes into each finger (Fig. 3), and those which use another principle namely that of stabilising the proximal segments of the fingers in flexion, a weak finger extension can be achieved with the long extensor muscles if the finger tendons are undamaged. It is not within the scope of this paper to give details[3], suffice it to say that if proper attention has been given to the indications in the various kinds of hands, both these principles can give good functional and reasonable cosmetic results.

The paralysis of the thumb is a major disability since the ability to oppose the thumb is the fundamental action on which both grasp and pinch are dependent. This disability is the result of paralysis of the median nerve, and is rarely seen alone, it usually occurs along with or after the claw hand. The commonest paralysis is probably still the combination of the ulnar and median nerves giving rise to the conjunction of the clawed fingers and unopposable thumb.

It is not necessary to dwell at length on the disability caused by a thumb which cannot oppose the fingers. There are several operations in use to correct this deformity. They usually achieve what they set out to do, namely to bring the thumb forward on the palm. Unfortunately, the thumb also requires to meet the fingers and close a grasp or pinch with some force depending on the activity performed. This force is supplied in the fingers, by the long flexor muscles, but in the thumb this does not help and pinch stabilisation therefore remains a problem

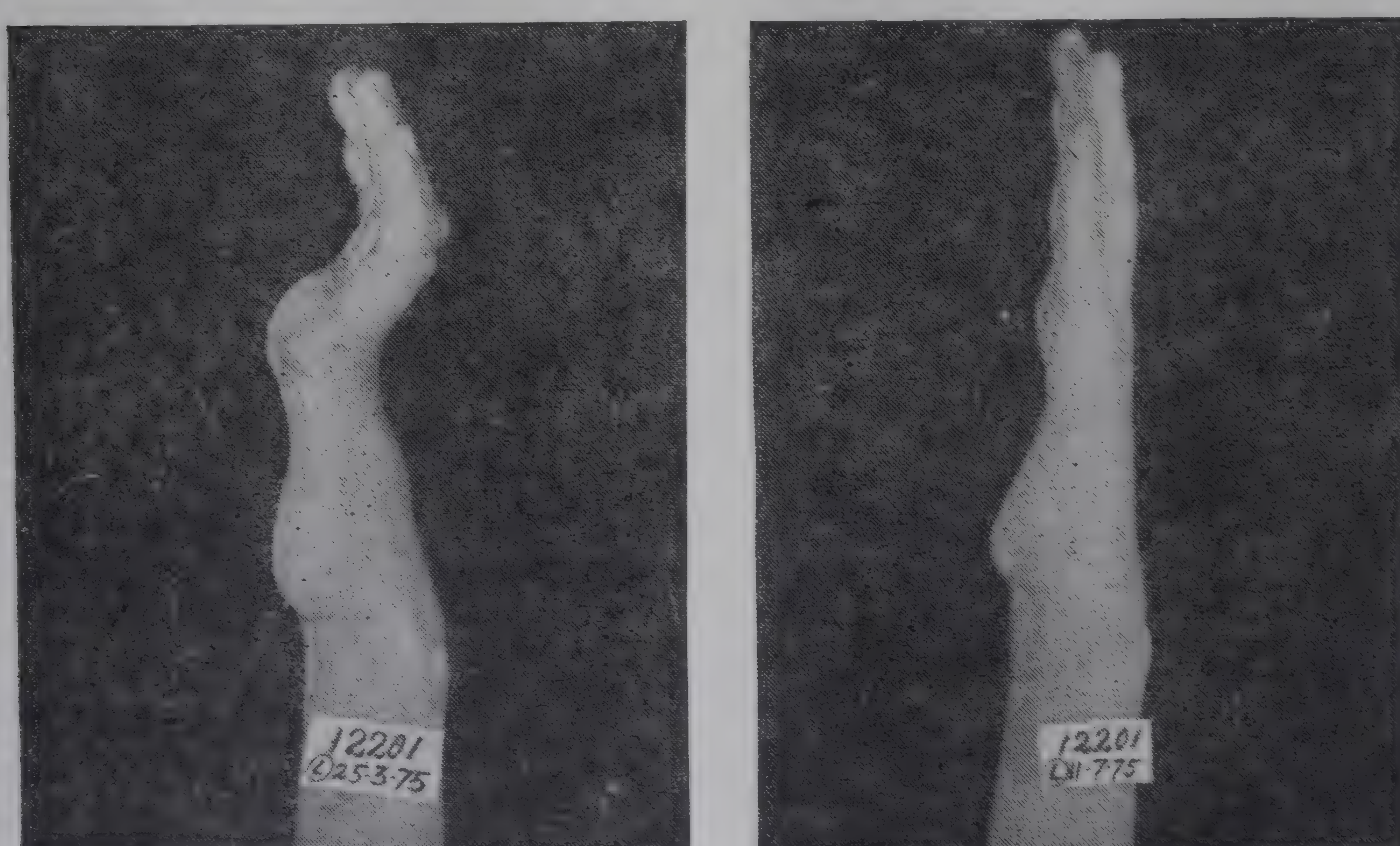

Fig. 3 The hand before and after a tendon transfer.

which has too many offered solutions, indicating that none of them are completely satisfactory! In practice however the result of the simple abductor replacement usually improves both function and appearance to the satisfaction of the patient (Fig. 4).

The triple nerve paralysis has been briefly dealt with earlier on. It involves all three nerves which supply the hand and a paralysis of these three nerves leaves so little that there will never be a good solution. However, for the person who requires only a 'paper weight' hand for sedentary and desk work, some improvement can still be offered (Fig. 5). For the farm labourer it is usually necessary to advise other employment.

There are some miscellaneous deformities corrections for which may be justifiably carried out for specific purposes. But the surgeon is well advised not to waste much time and money on reconstruction unrelated to a specific objective whether cosmetic or functional in each case.

The reconstruction of the foot

The two main nerves of the foot are also commonly affected, resulting in two main problems, the drop foot, where the patient cannot lift his foot at the ankle while walking and consequently walks with a high stepping gait, and the claw toes deformity, which is like the claw hand, namely extension of the first segment of the toe and acute flexion of the other segments.

The drop foot is a source of embarrassment to the patient because of the abnormal gait he assumes while walking. This can fairly easily be corrected simply by transferring the tendon of the muscle which pulls the foot inwards, and re-routing it so that it pulls the foot upwards. It is fairly easy for the patient to learn to use this tendon at the right time and the result is therefore satisfactory in most cases. This operation holds a useful place. It must however be realised that in many early cases of paralysis of this nerve it tends to recover, and therefore corrective surgery should be deferred until at least a year from the onset of the weakness during which time conservative measures should be tried.

The clawing of the toes is in itself a relatively minor problem, but it assumes importance when it is understood that this is probably an important factor in the predisposition towards ulceration of the forefoot, and also that it makes the wearing of closed shoes very difficult and likely to cause pressure sores over the knuckles of the toes. It can

Fig. 4 Correction of thumb paralysis to enable the function of grasp and pinch.

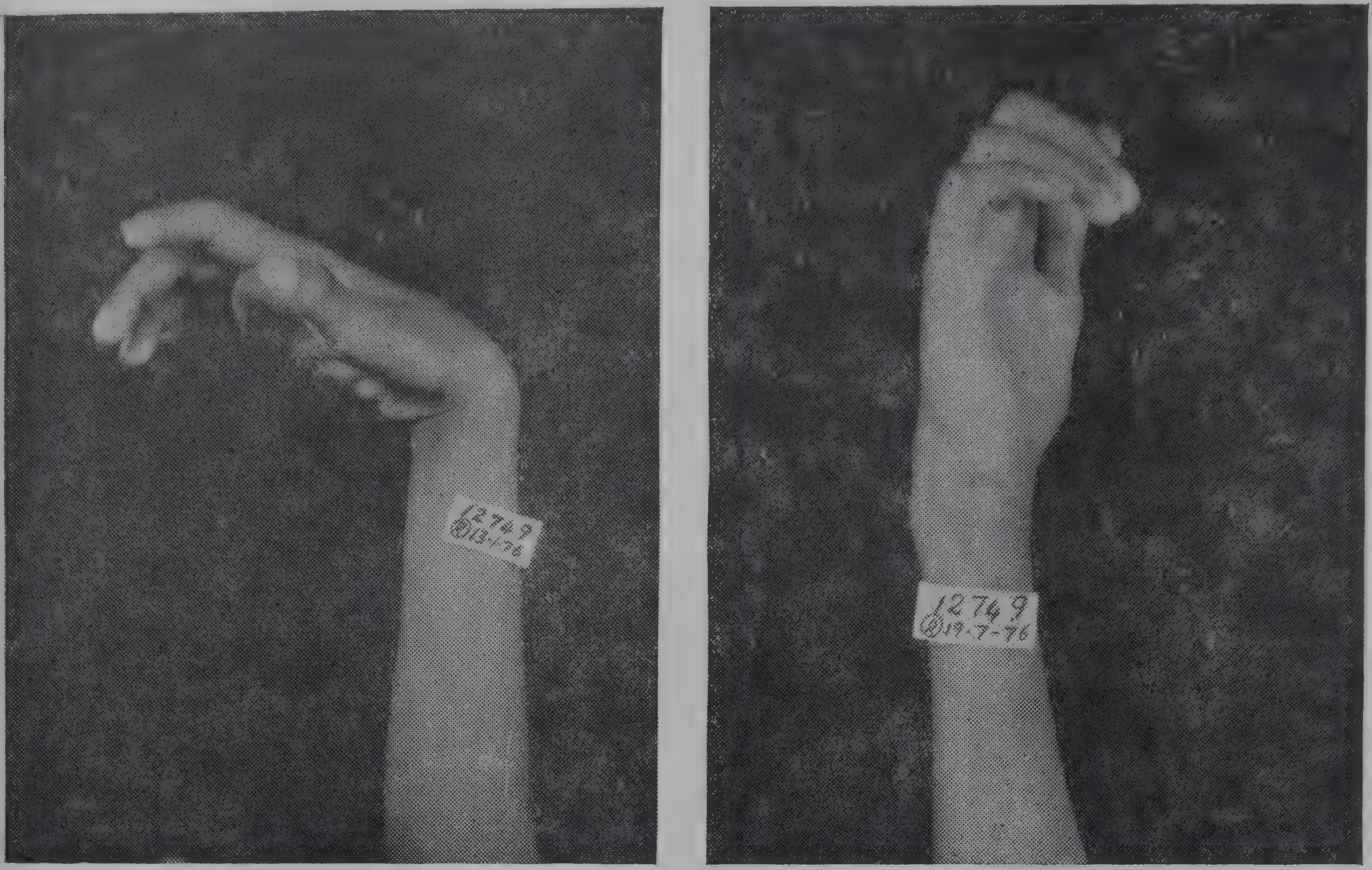

Fig. 5 Hand after corrective surgery for triple nerve paralysis.

also be quite easily and very successfully corrected by a simple tendon transfer to each of the toes (Fig. 6). This operation, if carried out early can contribute a great deal to the preservation of the foot from further secondary damage.

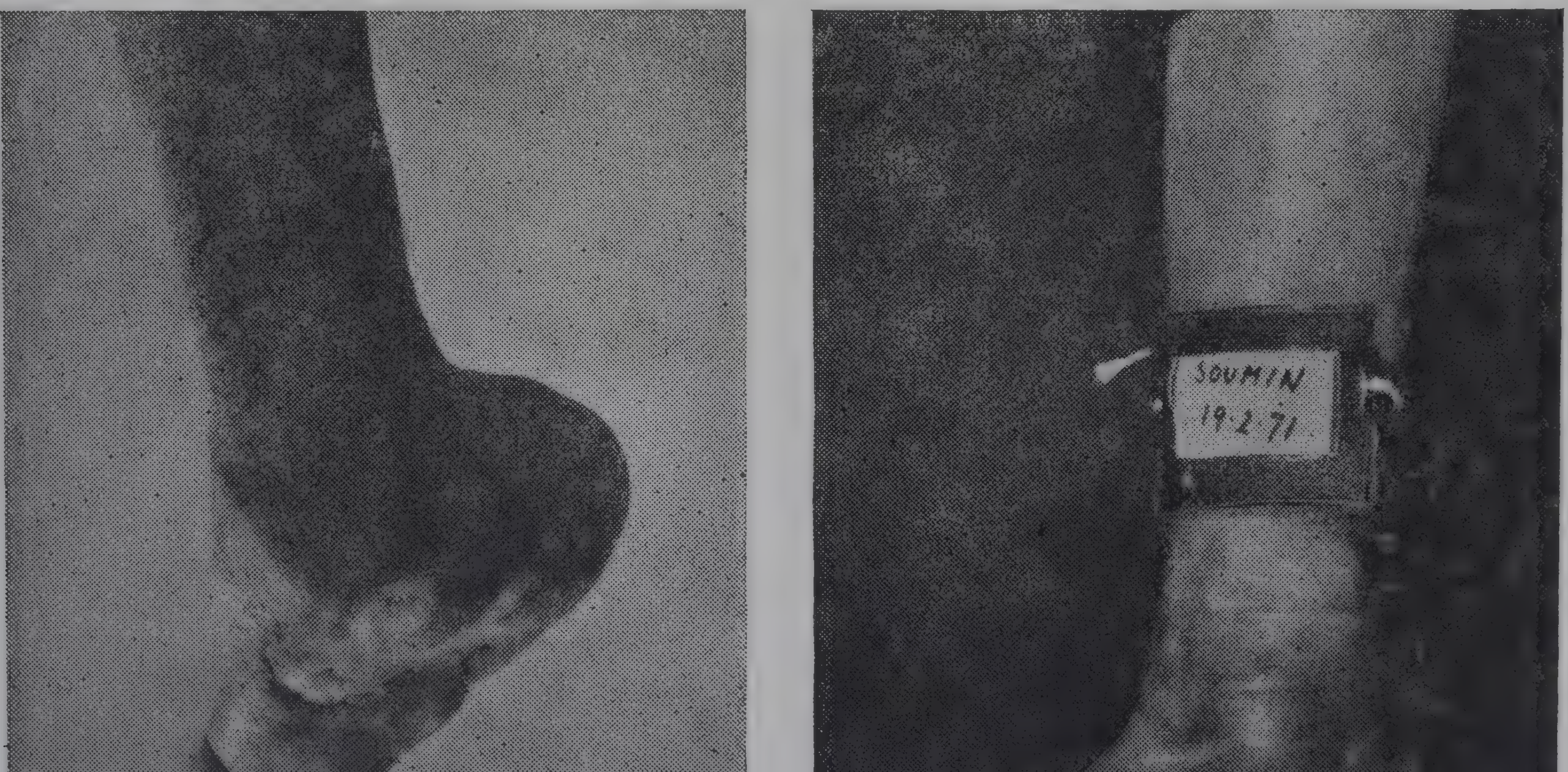

Fig. 6 Correction of clawed toes.

Corrective surgery has also a place in the more severe deformities of the foot which are occasionally seen as a result of painless sprains and fractures. Since these normally very painful injuries are neglected because the patient does not feel the pain, they tend to result in very serious deformities which render walking difficult.

When these deformities are recognised early, they can be very effectively treated by major bone-fixing procedures. These procedures are however costly to carry out because of the long periods of hospitalisation which are required.

The repair of the face

The most important procedure in the face is undoubtedly the correction of the paralysis of the muscles which close the eye. Failure of eye closure, especially when this is associated with a loss of protective sensation in the eye ball itself, can have the most serious consequences and can result in blindness developing. Here again several operations have been devised; they are of two types, the one which seeks to close the eye actively by a voluntary muscle contraction of the patient, and the second which aims at reducing the size of the opening of the eye lids and increasing their tension so that closure becomes almost a passive process and opening the active phase. Both types of operations are successful. The former however, while working beautifully when the patient contracts the transplanted muscle (Fig. 7), often remains inoperative because the patient does not use the transplanted muscle at the right moment. The latter therefore is likely to have more application. Some interesting new operations have been described consisting of implants of gold in the upper lid so that it falls by the action of gravity rather like a 'shut eye' doll. In our opinion based on a limited trial, this does not have a future. Attempts are now being made to implant plastic or stainless steel springs. These are not yet available in this country, but the principle seems to be worth working on.

It is very important to realise that the so called cosmetic procedures involved in facial surgery are as important for the patient's rehabilitation as any of the operations of the hand or foot. The patient cannot move freely in society unless his facial deformities are corrected. Today deformity of the nose rarely occurs *de novo*. When seen, the saddle

Fig. 7 Paralysed eye lids corrected by a tendon transfer.

nose deformity is usually in an old neglected case of many years standing. It is therefore reasonable to believe that this deformity and its correction is almost ready to be consigned to the history of medicine. However, there are still some cases which should be operated. Our own principle is to offer the patient the possibility of reconstruction and leave the decision entirely to him. Often he has got so used to the deformity that he does not ask for the operation, or he may be resident in a terminal care home, in which case there is really not much point as he is not required to take his place in society.

The repair of the nose is done through the floor of the nose approaching from under the upper lip. The nose is mobilised from behind and freed as much as possible. The cavity is lined with a skin graft. The resulting nose is soft and needs some support. This can be provided either by a prosthetic support inserted into the nose through the mouth opening, like a dental plate, or if, as is usually the case, the patient prefers it, a bone graft can be put in to support the ridge of the nose (Fig. 8). The bone graft is of course stiff and immobile not soft like a normal nose, 'this however need not be a cause of disability except perhaps to the younger and more amourously inclined patient!

Other procedures for the face include the replacement of eyebrows using hair bearing skin from the scalp. There are several modifications resulting in eyebrows of varying bushyness. Here again a delicate sense of judgement must be exercised by the surgeon in deciding the denseness which will be appropriate (Fig. 9). It must however be stressed that the hairs should be orientated in a natural way lest by injudicious placement the patient may have one eyebrow whose hairs are uplifted like a toothbrush advertisement, and the other which hangs down like a donkey's tail.

Face lift is another procedure available. It has been our principle here to perform this procedure only in the under 40 age group. The onset of wrinkles in the face is a physiological phenomenon and we have not felt called to interfere with the normal march of the years, but only to remove the precocious wrinkling which is the result of lepromatous destruction of the elastic tissue of the skin.

Earlobe trimming is a time honoured procedure which is almost ripe now for transfer to the annals of history since heavy infiltra-

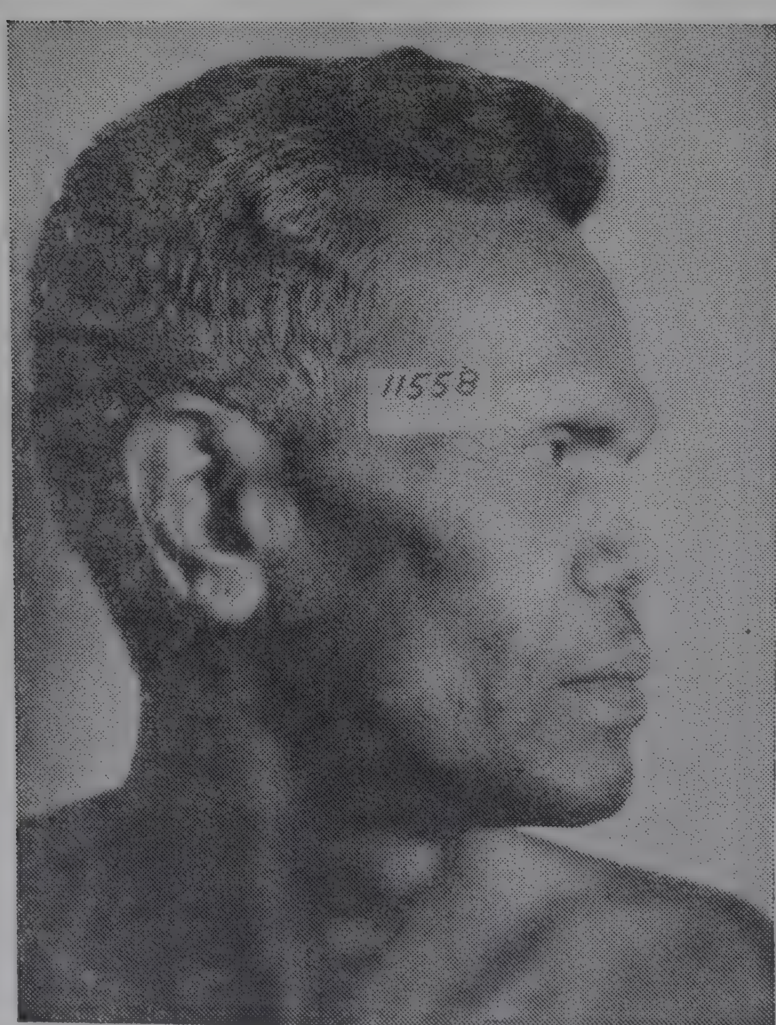

Fig. 8 Saddle nose deformity before and after correction.

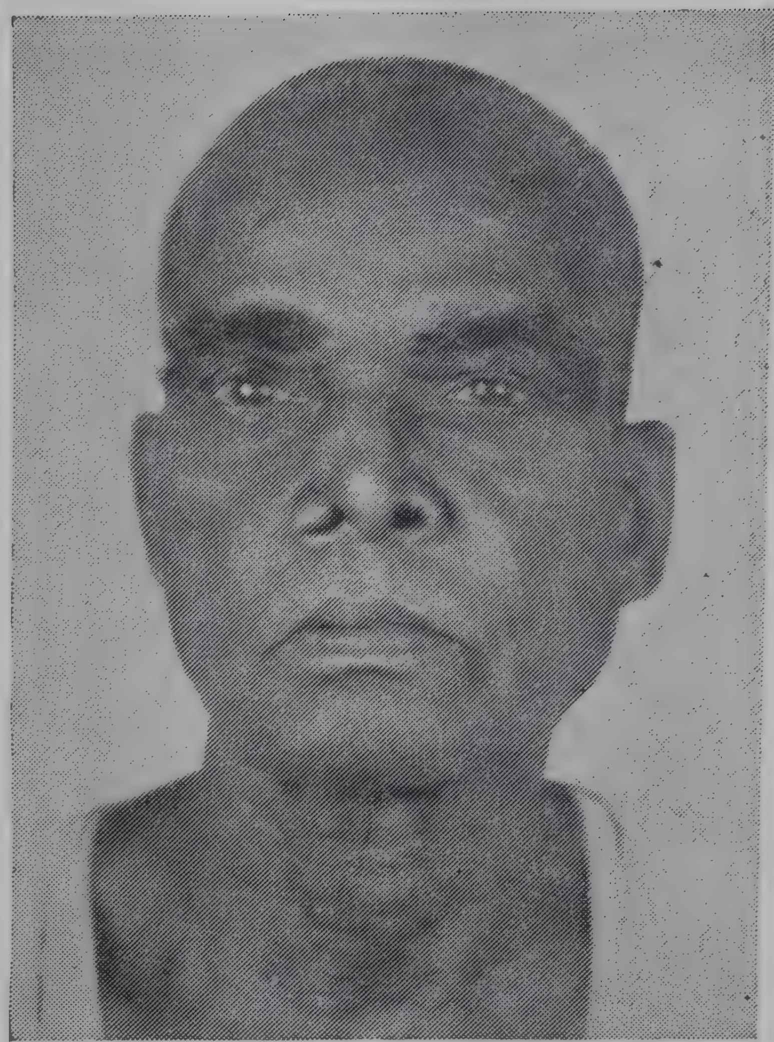

Fig. 9 Eye brows that contribute to the patient's rehabilitation.

tion, sufficient to call for surgical trimming, is a rarity at the present time.

Conclusion

Upto about 20 years ago Poliomyelitis provided the orthopaedic surgeon with much of his elective surgical material. Today after the systematic use of vaccines, most orthopaedic surgeons in developed countries have no knowledge of the paralytic deformities of polio. Even now, about 25 years after Salk's & Sabin's work on polio vaccines, this disease is still a major cause of disability and deformity in the developing countries. In leprosy, the search for suitable preventive vaccines is just beginning, and there are still formidable obstacles to be overcome before any hope of a break through can be entertained.

The present leprosy control programme of the Government of India is as up-to-date as it can be, considering the world's present understanding of leprosy. But the application of this programme over the last 20 years has produced a barely appreciable decline in the incidence and severity of deformity. There is however still hope that in the lives of many of the younger surgeons the deformities of leprosy may yet become nothing more than a sad memory of human suffering. Until that time however there will still be a great need for qualified and experienced and compassionate surgeons to apply their skills to this field of deformity. It is not necessary to have many centres, probably 5 to 6 may be all that is required but these centres should be properly and wisely distributed and should have properly trained expert teams, so that the best can be offered to the patient in each place.

If this is assured, surgery is still an essential service in any country such as ours where there is still a delay in the treatment of the early cases of leprosy. When due consideration has been given to indications and contraindications it still serves as an essential link between the treatment of the disease and the ultimate replacement of the patient in society and in useful and gainful employment.

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PREVENTIVE NERVE SURGERY IN LEPROSY

DINKAR D. PALANDE

Deformities and ulceration of the extremities is the picture of leprosy in the common mind. Involvement of the peripheral nerve trunks and their subsequent damage by the disease is the cause of these main disabling and stigmatising features of leprosy. It is fairly well known (first demonstrated by Dr. Khanolkar) that leprosy is primarily a disease of nerves, the main target cell being the Schwann cell which forms lining of the nerves. Preventive nerve surgery is a recent concept, and being recent, is still rather controversial. To find out why, it is necessary to have a historical perspective, a quick bird's eye view of the way advances in scientific knowledge in leprosy have occured—particularly those related to nerve damage and its recovery.

EVOLUTION OF THE CONCEPT

Prevention of deformity in leprosy has been a dream, an ideal so utopian that there has hardly been any talk or an article on this subject in the first half of this century, and if at all there was a thought bold enough to be transcribed, it was restricted to expression of a pious hope. The existing knowledge then did not allow anything more. In the nineteen forties D.D.S. was discovered—first drug found to act against the till then invincible Mycobacterium leprae. Other drugs did not follow—as they did for say tuberculosis—because this organism refused to be isolated, to grow and be studied outside the human body. Then came the successful work of Shepard, who showed that the bacillus could be grown in a mouse foot-pad. Advances in allied fields followed. The stress was on understanding the bacillus, understanding the disease, how it affects different body tissues and how the tissues react, bacteriology, pathology and immunology. For leprosy worker in the field Dr. R. G. Cochrane showed how to treat the disease. Influenced by him, the Orthopaedic Surgeon, Dr. Paul Brand discovered ways and means to cure deformities and to train doctors in those methods; he further proved that the deformities and ulcers and loss of fingers and toes are all because of damage to the nerves, by the disease. The Epidemiologist concentrated on how to diminish the 'case load' the infectivity, the incidence of the disease and the concept of Surevy, Education and Treatment, was brought into being. The vocational rehabilitationists led by Antonysamy (also influenced by Dr. Brand) stepped in and proved that it is indeed possible to do productive work and not injure an anaesthetic hand, an anaesthetic paralysed hand which has been reconstructed by surgery, provided proper training is given.

About the same time, in the early fifties, Carayon, a Neuro-Surgeon in Vietnam, saw his first case of neuritis in Hansen's disease. Naturally he concentrated on the problem of what happens to the nerve, why the nerve damage occurs at definite sites and what could be done to prevent it. From 1947 onwards Sunderland and others were bringing to light new knowledge on the anatomy of nerves, especially the internal anatomy. Carayon using all this new knowledge carried out his own exhaustive investigations, including contrast radiography, on the nerves in leprosy in Africa and from 1951 onwards he has been publishing a number of articles on this subject. He has demonstrated conclusively the role of external factors in progression of nerve trunk damage in leprosy and hence the rationale of the beneficial effect of surgical removal of these factors in preventing, reversing, or stopping further neurological damage. As most of these publications have been in French, there has been a time-lag for the knowledge from his work to percolate through the language barrier.

THE POSITION IN THE NINTEEN-SIXTIES

The position regarding nerve damage and its prevention in the late sixties can best be

summarised in the words of Mrs. Karat. Writing on the subject of preventive rehabilitation in leprosy (Lep. Review—January 1968), she stresses that, "Maintenance of the integrity of the function of peripheral nerve during anti-leprosy therapy should be the concern of every leprologist. This much-neglected, ill-understood and in most instances completely ignored, complication of the disease is the chief cause of morbidity in leprosy". She adds, "... Lack of such serious notice of nerve dysfunction in the mass treatment programmes results in a large number of casualties sustaining permanent injury to peripheral nerves resulting in anaesthesia or paralysis"; and further states that, "... This problem will continue to increase with the mass treatment programme until the medical and paramedical personnel begin to look beyond the results of skin smears for bacilli and the disappearance of skin lesions as their criteria of results of treatment, and take time and care to assess the peripheral nerve function during active anti-leprosy treatment". What were the methods then to prevent or reverse nerve damage? In the light of knowledge available then, Mrs. Karat restricts herself to recommending drugs like Chloroquine, and changing the specific treatment to thiosemicarbazone or Ciba 1906; Surgery was restricted to correction of deformity.

ADVANCES IN NERVE SURGERY

Relief of Pain—Prevention of deformity

Even though nerve surgery in leprosy was being done since the thirties, the operations were restricted to cases with established nerve paralysis and aimed at relief of intractable nerve pain. Because of lack of understanding of the internal anatomy of the trunk nerves, the procedures were also such as would damage the blood supply of the nerves exemplified by desheathing procedures and procedures which damaged the continuity of nerve fibres exemplified by operations wherein deep multiple incisions in the nerve were made. Carayon described his method of internal neurolysis respecting the nerve anatomy in 1962. Because of the intricate intermingling and anastamosis of nerve fibres between different nerve bundles (funiculi) within the same nerve, (Fig. 1) the procedure has necessarily restricted indications. In 1968 Vaidyanathan demonstrated a high percentage of sensory motor recovery in the ulnar nerve canal behind the elbow. (Within three month's paralysis: 71% complete Motor recovery and 50% sensory recovery of paralysis. Above 3 months duration 16% motor recovery and 14% sensory recovery. In all the rest of cases further progression of paralysis was stayed). This work was characterised by detailed analysis of 88 operations coupled with findings in 24 control patients. He demonstrated that earlier the surgery was done better was the result and in any case the results of surgery leading to nerve recovery in his hands were appreciably better than cases not treated by surgery. In the succeeding years, many publications followed, including by Galal Z., et. al. (1973)) Palande (1973)) Carayon (1972) and (1973)) Enna (1974) and others—demonstrating recovery of nerve function after surgery.

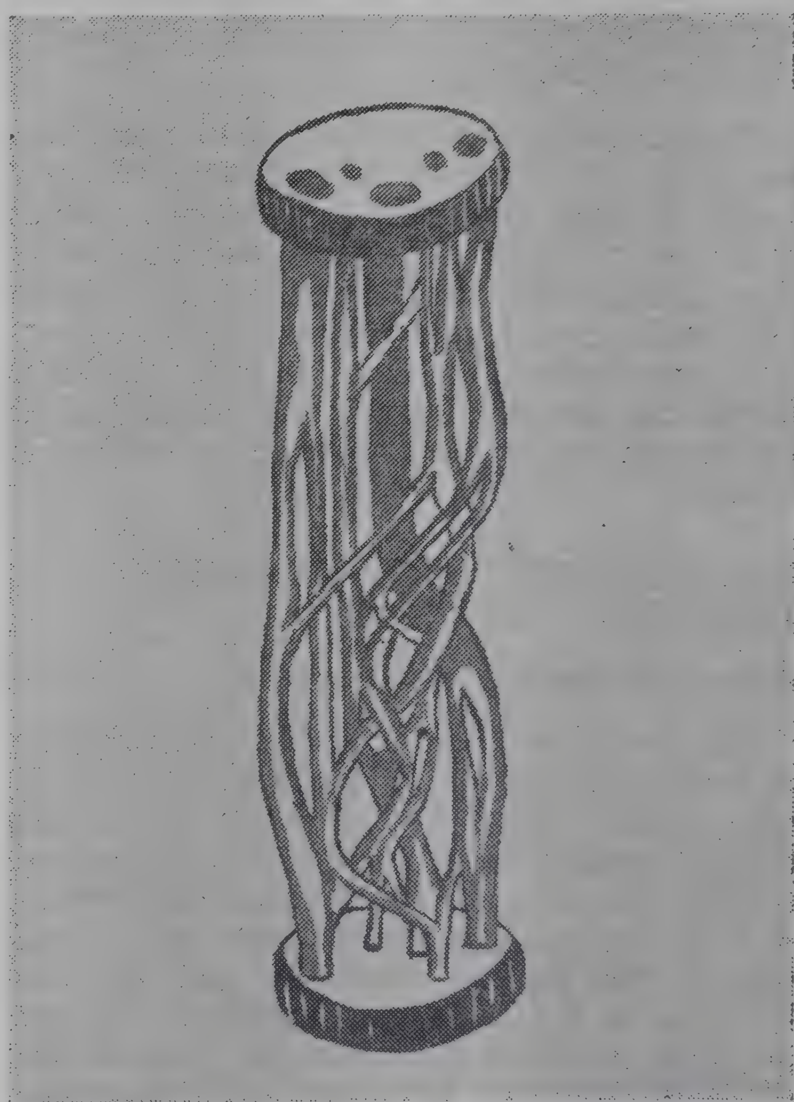


Figure 1. Internal anatomy of nerve showing the funiculi, inter-funicular connections and anastamosis (from Sunderland).

ADVANCES IN MEDICAL TREATMENT OF NERVE DAMAGE

Simultaneously there was progress in the medical management of nerve damage also. Newer ancillary drugs were found, tried, and some lingered on. Stanley Browne, Karat,

Ramanujam, Pearson, and many others contributed to the advance in medical management of neuritis. To-day, the value of prednisolone as an anti-inflammatory agent which diminishes nerve oedema, and controls the hyperactive cell-mediated immune response of hypersensitivity, and similar action of Thalidomide in E.N.L. episodes, is well recognised. Simultaneous administration of specific anti-leprosy drug is essential to control the growth of the organisms. Clofazimine combines as it were these needs of a specific drug and an anti-inflammatory agent; any additional amounts of corticosteriods when required are much less and need to be given for a shorter period. Karat, Pfaltzgraff and others have demonstrated a high percentage of success in prevention or reversal of nerve damage with these medicines. However, the success is much better in B.T. type of leprosy than in the BB and BL types.

A judicious combination of the medical and surgical measures of treatment of early nerve damage obviously is the ideal. What is the rationale of these treatment measures? The pathological and immunological basis of what happens inside a nerve trunk in leprosy has been dealt with in detail in other chapters. What are the anatomical and physiological factors on which preventive nerve surgery is based?

PHYSIO-PATHOLOGY OF NERVE DAMAGE IN LEPROSY

Pattern of Nerve Involvement

The peripheral nerve trunks are involved in leprosy at definite well known sites (Fig. 2) viz., ulnar nerve behind and above the elbow; median nerve proximal to the carpal tunnel; the posterior tibial nerve proximal to and in the posterior tibial tunnel below and behind the medial malleolus and its two branches in the calcaneal tunnels; the lateral popliteal nerve as it crosses the neck of the fibula proximal to its entry in the peroneal tunnel, and the radial nerve in spiral groove. The common anatomical features for all these sites are that the nerve distally passes through a rigid fibro-osseous tunnel, is near a joint and further it lies against bone. All these factors predispose to mechanical trauma by compression, friction and forced elongation. In case of the ulnar and posterior tibial nerves, there are some additional anatomical factors, and incidently these are the two nerves that are most commonly affected and lead to maximum morbidity in leprosy. In 4% of normal individuals the ulnar nerve dislocates completely around the medial epicondyle during flexion and extension of elbow, while in another 12% the dislocation is partial (Childress 1975). In both these cases the nerve is more vulnerable to external trauma. The posterior tibial nerve is accompanied by vessels which in majority of cases constitute the main blood supply of the foot. Both the nerve and artery pass first through the retromalleolar tunnel, then divide into medial and lateral plantar branches which pass again through two individual calcaneal tunnels. Secondary compression of the posterior tibial artery diminishes blood supply to the foot and also to the nerve since nerve is also supplied by its accompanying artery. Thus posterior tibial decompression is the decompression of the nerve as also that of its accompanying blood vessels aimed at restoration of blood supply to the foot as well as restoration of nerve function.

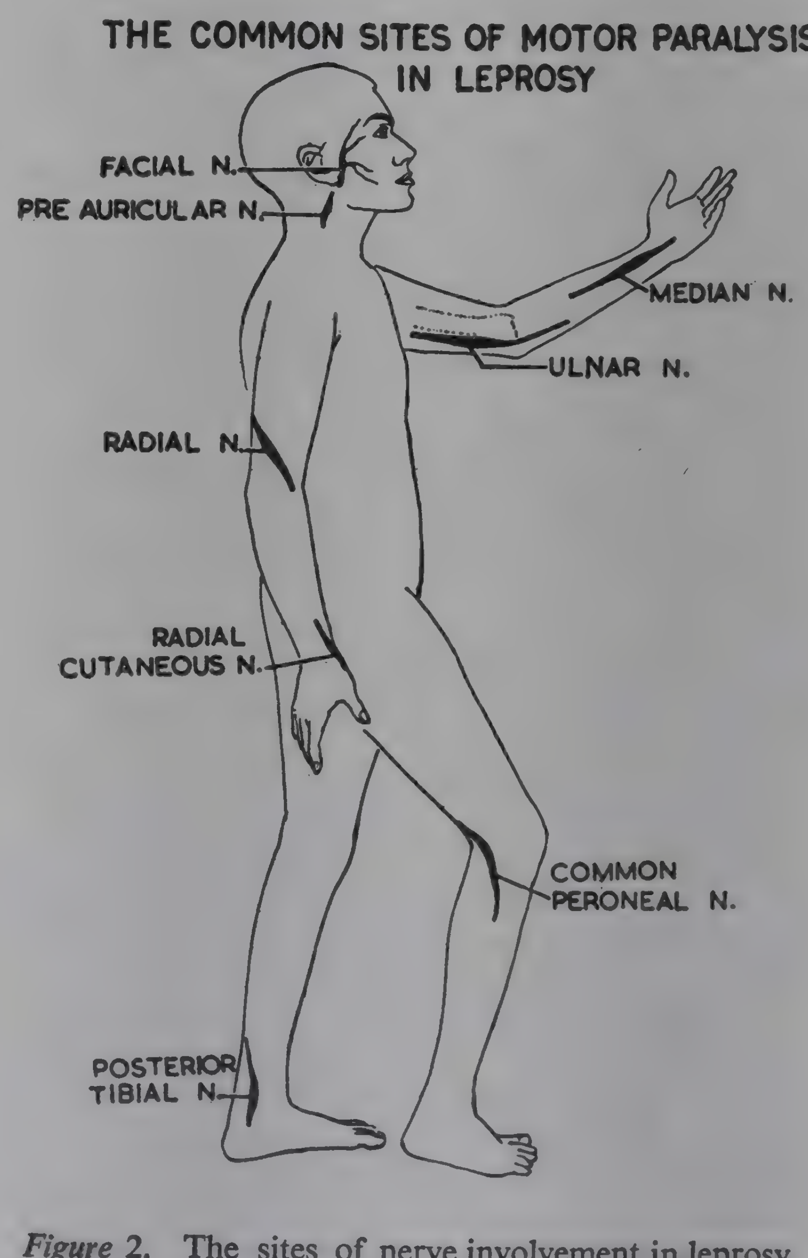


Figure 2. The sites of nerve involvement in leprosy (with acknowledgements to Dr. Antia).

INTERANEURAL CHANGES

Pathological changes of nerve involvement in brief are: invasion of the nerve by Mycobacterium leprae which is first evidenced by cellular infiltration and inflammation in a small involved segment. Accumulation of extra vascular fluid, i.e., oedema inside the nerve bundles increases the internal pressure. Because of the protective restricted permeability of the perineurium the infection remains restricted to the involved bundle, the other bundles being affected secondarily by the increased pressure within the whole nerve (Fig. 3). The increased pressure also affects the blood supply of not only the involved but the other nerve bundles also. There are then the usual changes of venous obstruction, slowing of circulation, increase of capillary permeability, and increasing oedema. Thus, a vicious circle is formed. The progression of inflammatory process and the resolution of oedema lead to increasing fibrosis. In the initial stages these changes are reversible. If relief is obtained, and the internal oedema and ischaemia relieved early, the nerve may recover. The bacillary load, has of course to be diminished and the immunological tissue reaction to be combated by suitable medication.

Figure 3. Median nerve decompression operative photograph showing abscess in the centre and normal bundles on either side. This patient did not have nerve paralysis. (With acknowledgement to Dr. Antia).

BLOOD SUPPLY OF A NERVE

There are four strata of blood supply of a trunk nerve: 1. The surface blood vessels; 2. The inter-funicular vessels; 3. The perineurial vessels and 4. The funicular vessels. The last are the first to be affected by the disease process, while the surface vessels are the first to be affected by tunnel compression.

ROLE OF EXTERNAL ANATOMICAL FACTORS

When the nerve becomes thickened because of the process described above, the external compression and mechanical traumatic factors come into play causing further damage:

1. In the affected segment there is a secondary inflammation of the surrounding tissues including that of the deep fascia which become thickened and compress the nerve.
2. At the level of entry in the tunnel, because of the nerve thickening there is a compression by the rigid tunnel walls, of the nerve and its vessels. The vascular block causes stagnation and arteriolar hypertension leading to oedema in the proximal segment.
3. Stretch trauma: normally the change in length required during joint movements is compensated for by sideward movement of the nerve. This is best exemplified by the ulnar nerve. Behind the elbow, during flexion of elbow, the ulnar nerve shifts medially to compensate for the increase in length which will otherwise be required. As the space inside the tunnel becomes diminished because of thickening of the nerve, this medial shift naturally gets diminished and the nerve is now stretched like a rope on a pulley. This causes damage to the blood vessels on and within the nerve. This is also the basis of the stretch sign which is elicited by demonstrating diminution of flexion range of elbow because of pain in ulnar nerve during that movement.
4. When the nerve is of dislocating type the thickened nerve is exposed to friction and the patient complains of pain as the nerve slides around the medial epicondyle during elbow flexion. There is injury to the nerve and hence to its surface blood vessels.
5. Below the elbow, the ulnar nerve passes through the Flexor Carpi Ulnaris tunnel as the humeral and ulnar fibres of the muscle join together (Fig. 4). Contraction of this muscle causes compression when the nerve is thickened

and inflamed. This also is the rationale of the muscle compression sign—pain in the nerve on muscle contraction.

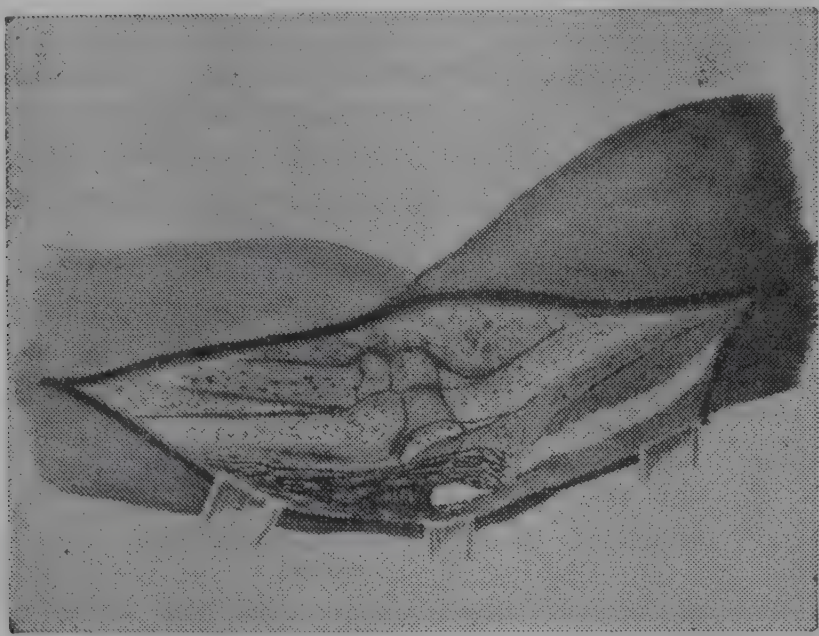


Figure 4. An artist's impression of the ulnar nerve (in white) thickened above elbow passing behind the medial epicondyle (upper tunnel) and entering the front of the upper forearm where it passes through the two origins of the flexor carpi ulnaris muscle (lower tunnel). The upperpart of the roof of the tunnel is removed ; the lower part of the tunnel can be well seen.

6. In case of the posterior tibial nerve, its main artery of blood supply comes from the accompanying posterior tibial artery which is also often the main artery of supply to the sole of the foot. Compression of this neuro-vascular complex secondary to nerve thickening, results in diminution of blood supply to the nerve by compression of the posterior tibial artery (Fig. 5).

7. The surface blood vessels in the median and lateral popliteal nerves are particularly vulnerable to compression at the respective sites of involvement.

Once all these external anatomical factors start acting, secondary to nerve thickening (due to intraneural oedema) again a vicious circle is established; infection—internal oedema—nerve thickening—increased external pressure by tunnel roof and nerve coverings—compression of surface vessels—blood stagnation and proximal arteriolar increased pressure—more oedema of the nerve. Specific anti-leprosy drugs and anti-inflammatory drugs, are essential to combat the internal pathological process. Surgical relief is necessary to eliminate the above described external factors which continue and compound the damage started by invasion of the nerve by Mycobacterium leprae and the attendent tissue response. In the initial stages, to an extent, the relief of nerve oedema by drugs is probably sufficient to stay the progression of the nerve damage. However, the external factors must be relieved before the critical point of irreversibility of nerve damage is reached to enable the nerve to recover.

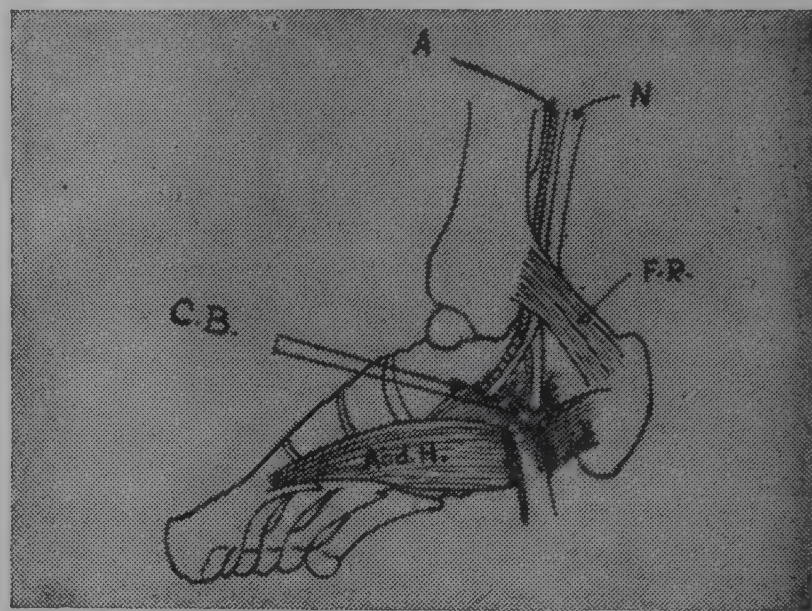


Figure 5. Posterior tibial nerve and artery passing through the retromalleolar tunnel behind the flexor retinaculum and its two main branches entering the calcaneal tunnels.

A=Artery, N = Nerve, F.R. = Flexor Retinaculum, C.B. = Calcaneal Bands roofing the calcaneal tunnels.

INDICATIONS OF SURGERY

There are certain clinical signs and symptoms which indicate progression of nerve damage and the increasingly coming into effect of external compression factors. These are:

1. Progressive nerve deficit while under full medical treatment;

2. Sudden increase in the nerve deficit indicating active increase in the internal nerve pressure; which may be due to sudden oedema or an abscess formation;

3. Increase in the intensity of pain and tenderness in the nerve inspite of medical treatment;

4. A positive stretch sign, not relieved by medical treatment;

5. A positive compression sign; this is elicited by asking the patient to close the fingers and flex and medially deviate the wrist forcibly, thereby contracting the flexor carpi ulnaris and the flexor superficialis muscles both of which form the roof of the ulnar canal. When pain is elicited by this maneuver the sign is positive;
6. Pain on flexion of elbow as the nerve slides forward with a click, in case of the dislocating ulnar nerve.

All these above indicate the actively coming into force of external traumatic factors; at this time, the earlier surgery is done, the more will be the likelihood of nerve recovery. Ofcourse, before these factors come into play, there is no need for surgery and routine specific and anti-inflammatory treatment together with rest of the nerve by appropriate splinting is enough and adequate. In case of posterior tibial nerve, nerve recovery with medicines alone is rare, and hence early surgery is advocated. Similar is the case with median nerve paralysis. In general, the insidious nature of nerve involvement and slow onset of pain and paralysis cause delay in the patient seeking treatment.

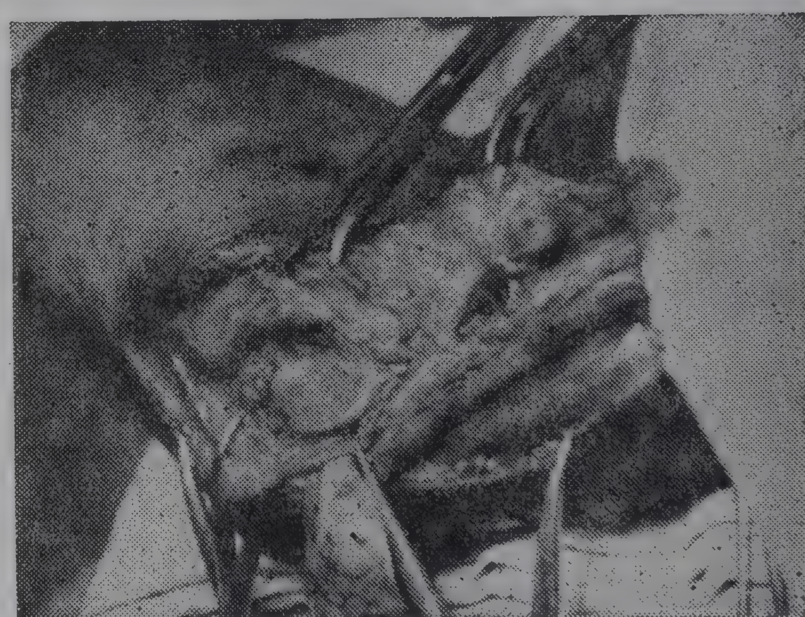
SURGICAL PROCEDURES

To-day, the surgical procedures are restricted to essentially two main aims:

1. Relief of external compression and preventing further trauma; and
2. Relief of internal ischaemia and pressure.

The first is achieved by incision of the roof of the compressing tunnel, of the compressing external coverings of the nerve (the false sheath formed by the deep fascia) and epicondylectomy for the ulnar nerve. When the epicondyle is removed, the ulnar nerve now lies laterally in a neutral plane as far as elbow movements are concerned so that it neither has to shift, nor elongate, nor dislocate during elbow movements. The second aim is achieved by median epineurotomy (incision of the nerve sheath) and by fascicular (inter-funicular) neurolysis. External decompression including incision of the tunnel roof can be carried out in an ordinary operation theatre with minimum of instruments and surgical skill; but with disproportionately good results when done early as demonstrated by Vaidyanathan. Epicondylectomy needs a little more surgical skill. Median epineurotomy and fascicular neurolysis have to be done with a delicate hand by a well trained surgeon, preferably using magnification during surgery so as to ensure that there will not be any damage done to the nerve by surgery. (Figures 6-A, B, C, D.)

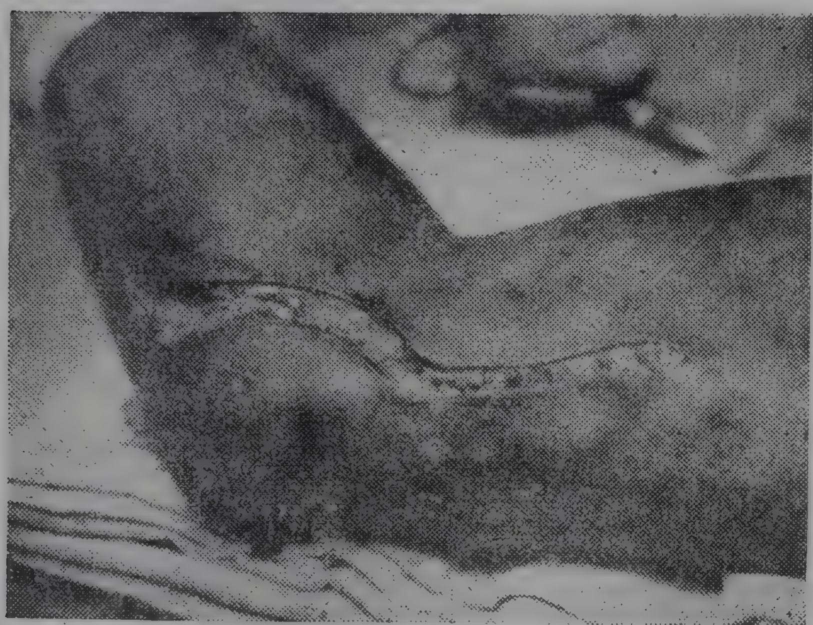
6A



6B

For all these, the patient has to stay in the hospital for not more than one week. In case of epicondylectomy, he has to have an elbow splint and the elbow in a sling for 2 weeks. The lesser the nerve involvement, as shown by sensory-motor deficit, and the earlier the surgery done, quicker are the results seen in terms of nerve recovery. When the nerve is completely paralysed, it takes a maximum of one year to get complete recovery after surgery.

6C



6D

Figure 6. Operative photographs :

(A) Showing the exposed thickened ulner nerve above the elbow, the bared medial epicondyle and the tunnel behind it.

(B) The Epicondyle has been removed.

(C) The raw bone has been covered over by the Flexor Muscles' origin and restricted fascicular neurolysis has been carried out on the ulnar nerve above the elbow. Note the nearly normal nerve below the elbow and its marked thickening above the elbow.

(D) The incision being closed.

WHY PREVENT NERVE DAMAGE?

Is prevention indeed better than cure? What is actually involved? Deformity is the main stigma in leprosy. Once a nerve damage is irreversible, the sensory loss leads to ulceration, loss of digits, involve bones, foot deformity and loss of use of the extremity; motor power loss results in disability, e.g. inability to use the hand or the thumb. Sensation plays such a major role in not only protection, but also in monitoring and successful execution of the intricate hand movements in daily life that previous to the successful experience of reconstructive surgery in leprosy most hand surgeons were reluctant to operate on a hand with total sensory loss. Well established sensory loss cannot be restored, only the motor coarse movement pattern can be restored by reconstructive surgery of paralytic deformity. Other measures are, training on how to use the anaesthetic limb and provision of protective gloves and footwear.

All these measures are costly, demand well trained personnel, are time consuming and are not always successful. Reconstructive surgery's success, apart from the quality of the surgical team, depends on how old, how chronic the deformity is, on the absence of joint stiffness and other complications. Its availability is also restricted. Preventive treatment of deformity involves—early detection of neuritis with or without deformity, availability of drugs (Thalidomide is available with difficulty, Clofazimine is costly, corticoids are double edged weapons and need great care in their use), availability of a Surgeon who has to have the same skill but less training than that required for reconstructive surgery, low cost in hospitalisation and last but the most important is awareness that deformity can be prevented, nerve involvement and damage can be reversed provided the cases are seen early, examined and detected early and treated early.

PRESENT STATUS OF NERVE SURGERY

Reasons for Controversy

There are conflicting claims, differing operative procedures, inadequate corelation with the type of leprosy, insufficient follow-up and differing criteria of assessing the improvement of nerve function all of which generate controversy. As Dr. Antia points out (1973) ... "One of the reasons for such varied results (of surgery) may be an inadequate appreciation of the existing pathology and of the physical factors responsible for nerve damage. These vary with the type

of the disease and with the stage, in the same individual". Then it is very difficult to find two comparable cases of nerve trunk involvement in leprosy because of the extreme variegated pattern of the disease and its manifestations, and the known occurance of relapses and exacerbations in the lepromatous side of the disease. Even the two ulnar nerves of the same patient are rarely comparable, either only one is involved or if both, the degree of involvement is different. The skin lesions and the nerve lesions do not also necessarily show identical histological pattern in the same patient. Finally, one cannot be certain if a nerve would have recovered without treatment, with medical treatment, or with medical treatment and surgery. A solution of this problem can only be by maintaining detailed records of a large number of cases over a long period so that there is a long-term follow-up; an adequate number of comparable cases may then be found to arrive at satisfactory statistical conclusion. This will necessitate a prospective study done at different centres, the data then being pooled for statistical analysis. This will be a long-term project. Pending the above, the benefits of the present knowledge should be extended to all patients.

SUMMARY OF RECENT WORK ON PREVENTION OF NERVE DAMAGE IN LEPROSY

The results of treatment to prevent or reverse nerve damage in leprosy, considering some of the recent work, are as follows:

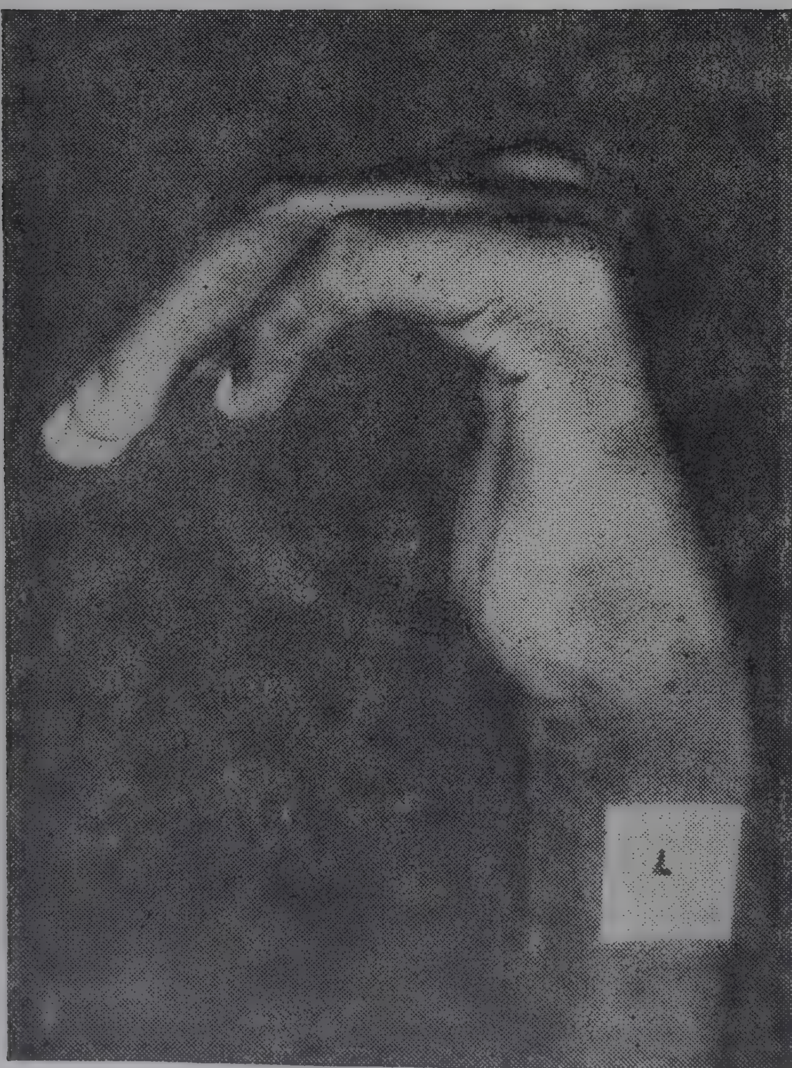
Roy E. Pfaltzgraff has shown (1972) 70% improvement in the B.T. group and 52% in the B.B.—B.L. group of patients treated with Clofazamine and Prednisolone. Karat (1973) has also shown similar results, in all types of leprosy. Carayon (1973) has demonstrated recovery in 79% of cases operated within 3 months and in 65% when operated within the first 6 months. N. Pandia and Antia (1975) have obtained sensory recovery in 91% of their cases of which 50% had total recovery, and motor recovery in 76% of which 12% had total recovery. My own results are: in the patients treated during 1970-1975 medically, the results are in T.T.—B.T. group there is 80% recovery in motor and 66% in sensory nerve function; in the B.B.—B.L. group both motor and sensory recovery is 70%, while in the L.L. group in 58% there is sensory and motor recovery. In the surgically treated patients (who ofcourse, had medical treatment also) in the T.T.—B.T. group, there is motor recovery in 65% and sensory recovery in 45%. In the B.B.—B.L. group, the figures are similar. In the L.L. group, there is motor recovery in 77% and sensory recovery in 68%. This shows that recovery has been maximum in the T.T.—B.T. group in cases treated with medicines alone while the cases who had surgery in addition, when indicated, showed maximum recovery in the L.L. group. In all these cases surgery was done when indicated by the presence of signs, mentioned previously, continuing or increasing in intensity inspite of medical treatment (Figs 7 & 8). Carayon (1977) agrees that the B.T. group shows excellent recovery with medical treatment and surgery in these cases is rarely indicated, except when there is an acute sudden progression of nerve damage as seen in the case of a nerve abscess.

There is a positive corelation found by all workers between the incidence of recovery and the duration of nerve damage. The above data quoted is predominently for the ulnar nerve. I have had recovery in 75% of cases after median nerve decompression. All the recoveries were in cases operated within 2 months of paralysis. In the case of the median and lateral popliteal and posterior tibial nerves, there is even more urgency for early measures since the blood supply of these nerves is earlier affected. In case of the lateral popliteal nerve the blood vessels are often compressed against the bone by the nerve because of anatomical relationships. The incidence of nerve recovery reported for the posterior tibial nerve is low (6 recoveries reported by Carayon) because early operation was not done, the surgery of the posterior tibial neuromuscular complex being aimed for a long time at improving blood supply to the foot in the treatment of plantar ulcers.

My own recent experience of operating on early posterior tibial nerve paralysis is very encouraging. Out of 10 posterior tibial nerve decompressions done in early nerve paralysis this year there has been sub-total recovery of sensation in 7. Since loss of sensation on the sole of the foot and the slowly increasing poserior tibial nerve pain often goes unnoticed, the patient does not report early enough. Creating awareness that nerve involvement if detected early can be relieved by prompt treatment is the only way to get early cases.

7A

7B



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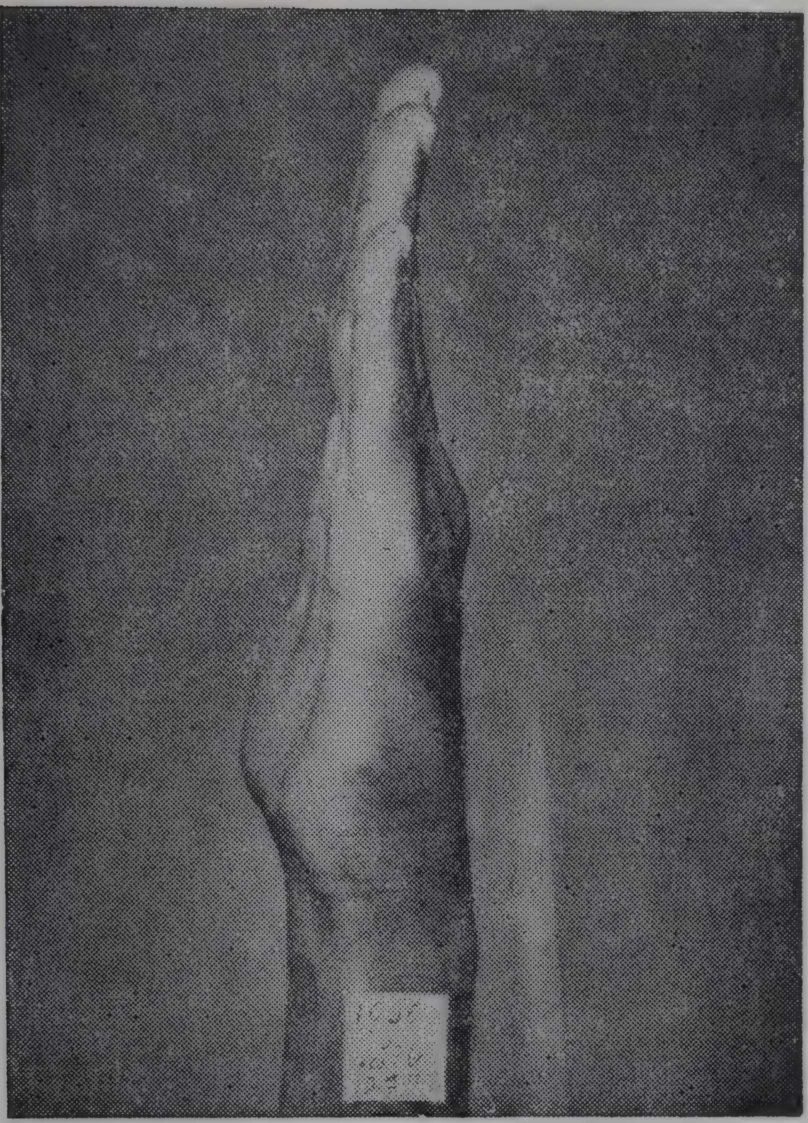

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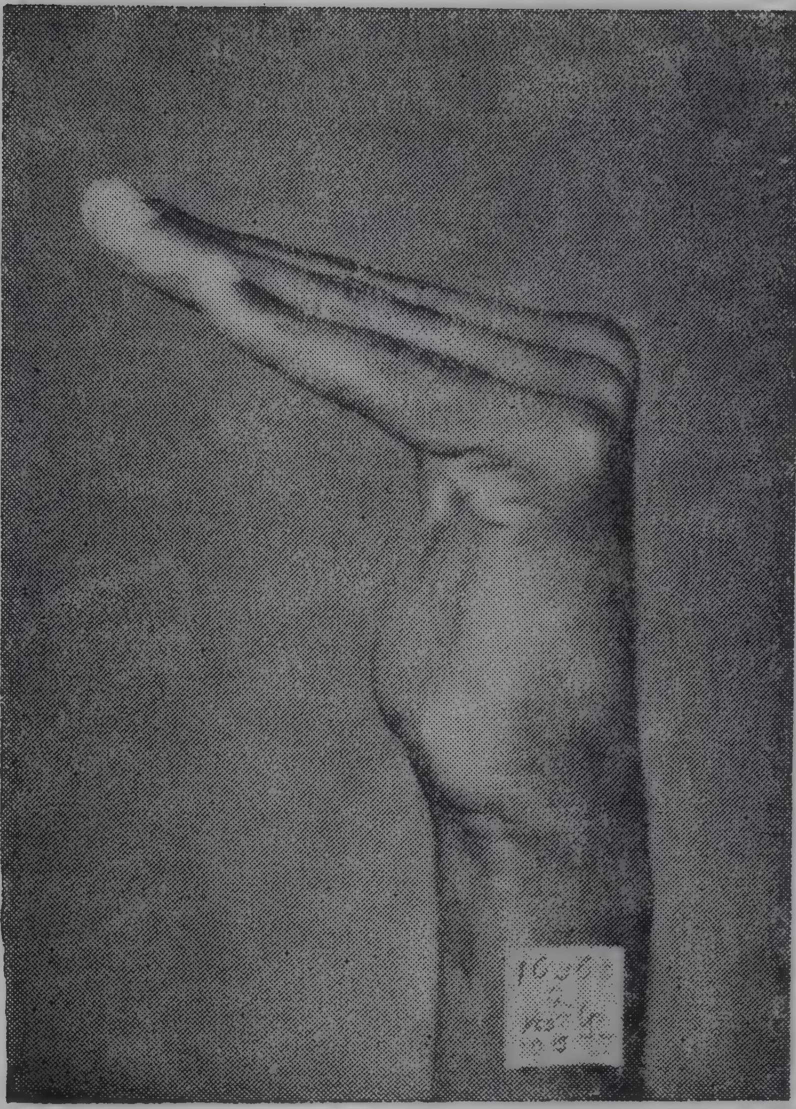
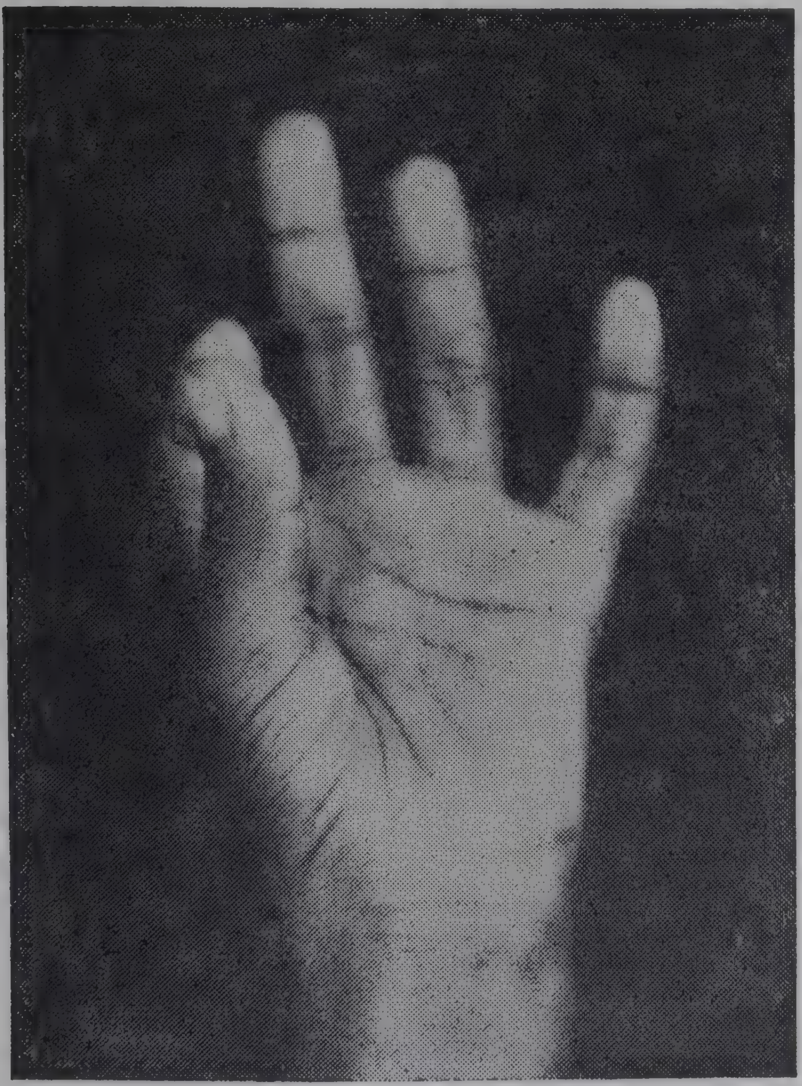


7F

Figure 7. Preoperative photograph (A) Open hand, (B) Side view, (C) Attempted lumbrical position showing deformity of ulnar nerve paralysis and (D), (E) & (F) photographs 2 years after nerve decompression and fascicular neurolysis demonstrating complete nerve recovery being maintained. The type of disease was L.L. and duration of ulnar paralysis 2 months.



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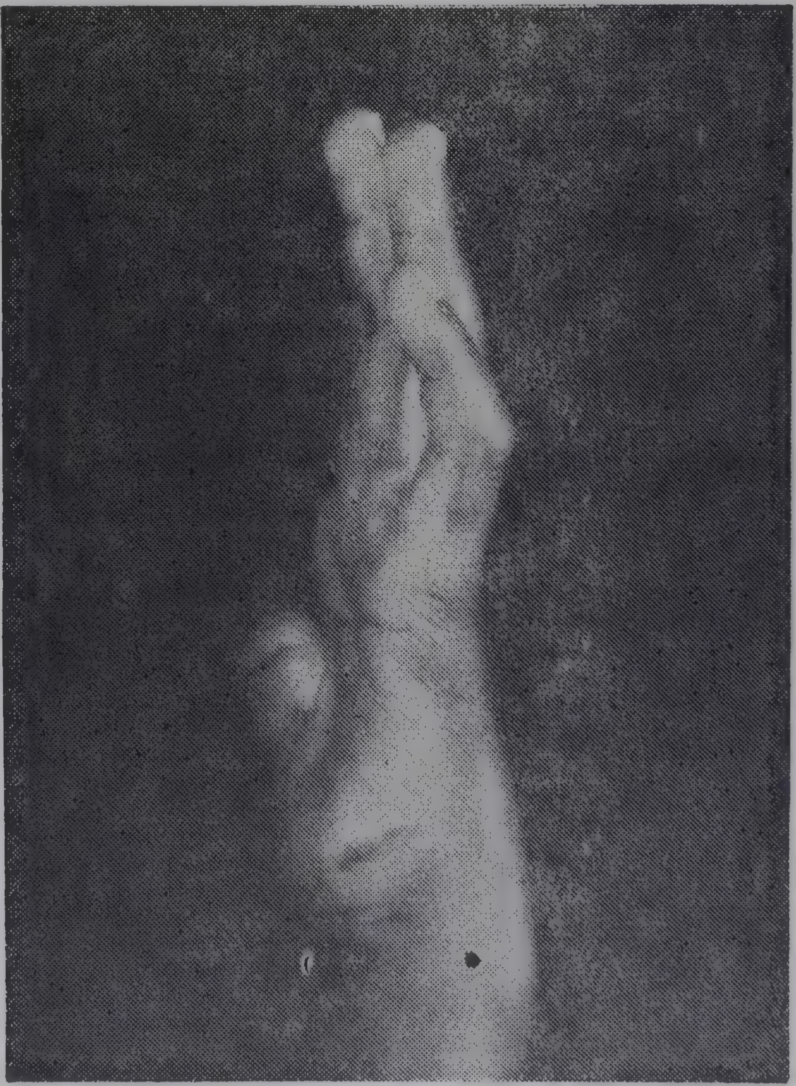

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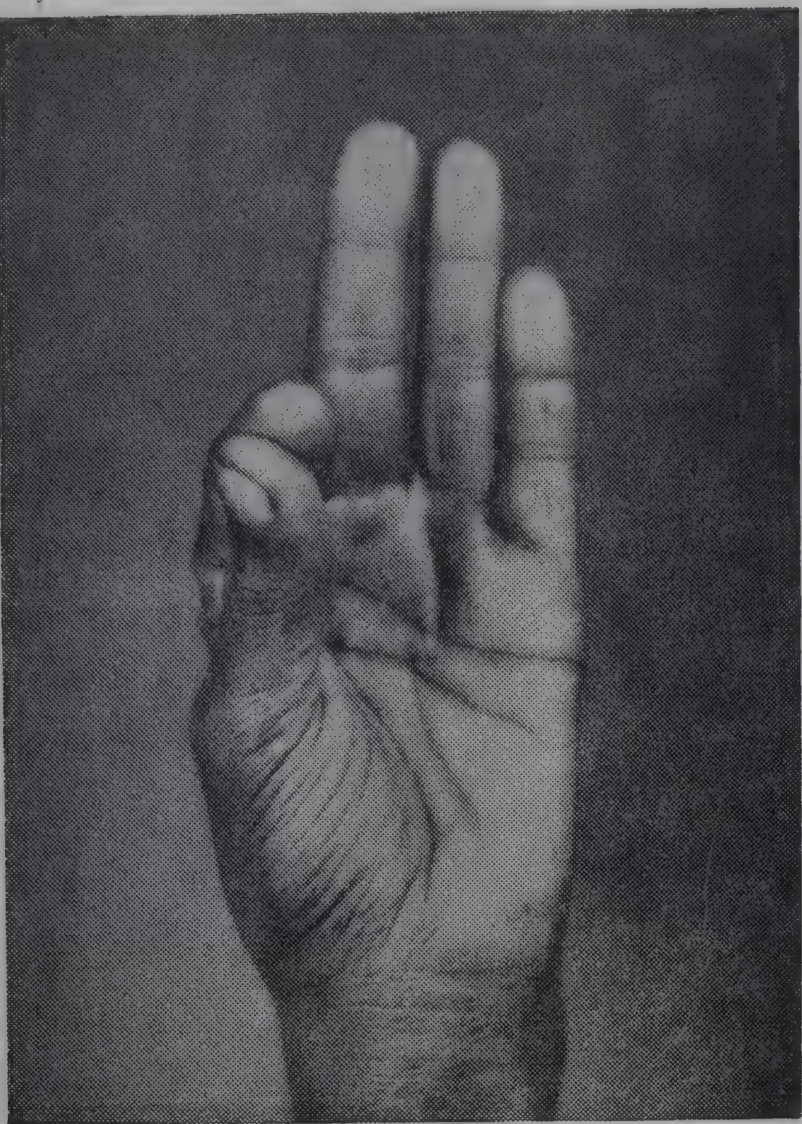

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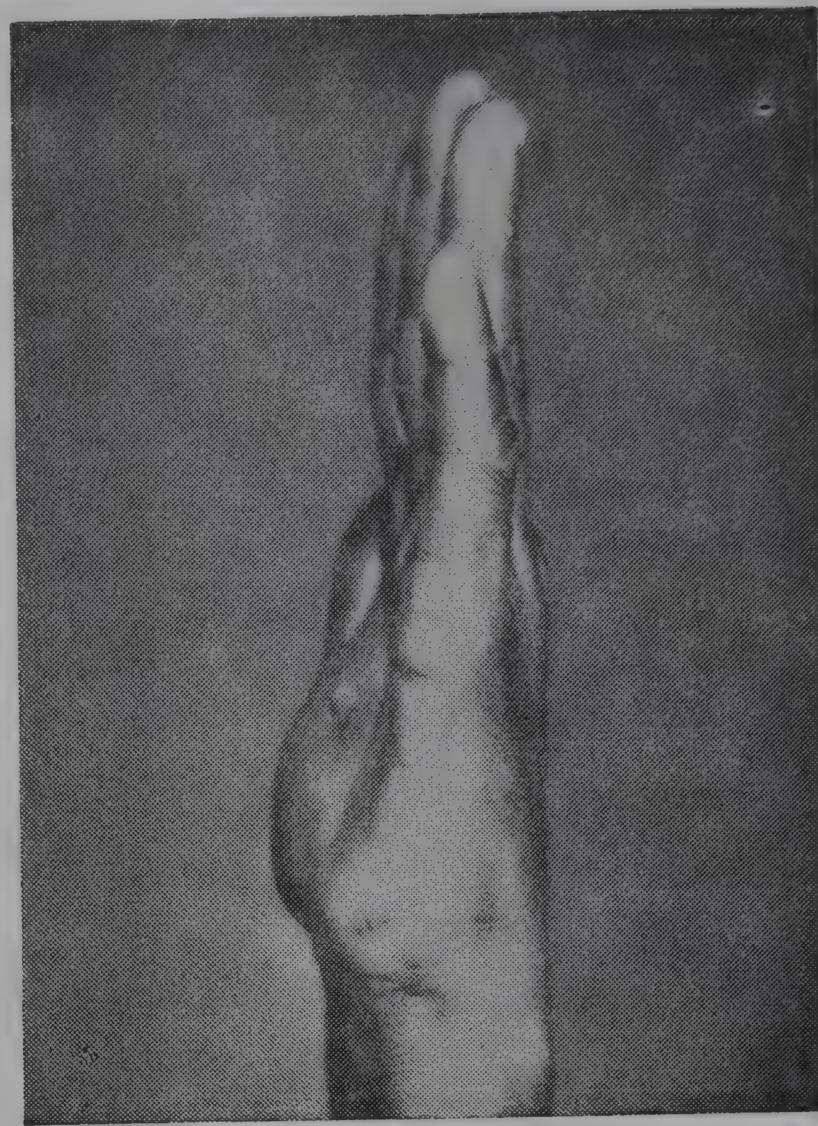

8D

Figure 8. Preoperative (A) & (B) and two year postoperative (C) & (D) photographs of a L.L. patient with ulnar median paralysis, showing full recovery, after ulnar and median nerve decompressions, being maintained. Note the deformity and wasting of the hand in (A & B) and the normal hand and thumb (C & D). The ulnar nerve paralysis was of 7 months duration and the median nerve partial paralysis of 2 months duration.

CONCLUSION

Preventive nerve surgery is based on sound scientific principles; the benefits are outstanding, but its scope is not yet well recognised. The prevention of deformities by medical and surgical measures is today possible and this knowledge has to be extended to all concerned in the field.

The priorities in the leprosy control and treatment programme have to be reviewed and a place found therein for a programme of preventive rehabilitation. This will essentially imply early detection of nerve damage in the field, referral of these patients to a base hospital where together with minimal hospitalisation required the nerve damage will be assessed and the needed treatment instituted. Thus early nerve damage will get treated before the patient gets dehabilitated because of the deformities and ulcerations subsequent to nerve damage. Minimal nerve surgery can be done at any hospital. These measures alone can reduce by half the number of patients that would need reconstructive surgery and rehabilitation later on.

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IMMUNOTHERAPEUTIC APPROACHES TO LEPROSY—PERSPECTIVES AND POTENTIAL HAZARDS

WARD E BULLOCK

I. WHY THE NEED FOR AN IMMUNOTHERAPEUTIC APPROACH TO LEPROSY ?

The introduction of diaminodiphenylsulfone (DDS) as a cheap and effective drug for treatment of leprosy has done much to dispell the therapeutic gloom that prevailed prior to 1948. However, it is too much to expect that DDS or any other single agent can consistently render non-viable all *Mycobacterium leprae* in patients who are highly bacilliferous. In fact, relapses due to the appearance of DDS-resistant *M. leprae* were first detected in 1964 and since then, the prevalence of resistance has been increasing. In Malaysia, at least 2.5% of lepromatous patients treated with DDS harbor organisms resistant to this drug and in Ethiopia, approximately 15% of treated patients are estimated to have resistant leprosy bacilli (1).

Important new drugs such as rifampin and B-663 now permit combination antibiotic therapy to reduce the probability that some of the *M. leprae* in lepromatous patients will become drug resistant. However, there is the added problem that viable bacilli can persist in tissues for long periods even in the presence of DDS and rifampin therapy to which the organisms may remain quite sensitive (1). This persistence of drug-sensitive *M. leprae* can be likened to a state of "bacterial hibernation" in which the metabolic functions of the bacillus are so slow that conventional combinations of antibiotics become extremely inefficient at interrupting these processes. Thus, unless host defense mechanisms are capable of eradicating these sleeping bacria, there is the chance that some may reactivate an infection when the pressure of antibiotics is removed. Unfortunately, the host response of lepromatous patients is poor and they tend to relapse at rates varying from approximately one to six percent per year (2).

The question then is how to assist patients in ridding themselves of *M. leprae* in the situation where one may be dealing with organisms resistant to multiple drugs or with drug-sensitive persistors. Certainly, the discovery of new chemotherapeutic agents may assist in this task. However, it would be a superb achievement if in some way we could stimulate the cell mediated immunity (CMI) of lepromatous patients to the point where it could dispose of the leprosy bacillus efficiently.

To date, all attempts to improve the immune response to *M. leprae* in lepromatous patients have been somewhat simplistic since we don't yet fully understand the extraordinary complexities of the human host defense against facultative or obligate intracellular pathogens. What is known about such infections is that macrophages derived from circulating blood monocyte precursors, and lymphocytes, are pivotal to the defense. In leprosy, defective function of both cell types has been reported. Some have claimed that there is a specific defect in the capacity of macrophages from lepromatous patients to kill and digest *M. leprae* (3). Others have presented evidence against this claim suggesting indirectly that the fundamental defect may be found within the thymus-dependent (T)-lymphocyte or at the level of cell-to-cell cooperation between T-lymphocytes and macrophages (4).

Many studies have shown that patients with lepromatous leprosy are generally skin test negative to Dharmendra or Mitsuda preparations of *M. leprae*. Furthermore, T-lymphocytes from lepromatous patients do not "recognize" antigens of the leprosy bacillus as shown by a failure to undergo blast transformation when exposed to *M. leprae* in the test tube. In attempting to interpret these results, some have argued that lepromatous patients have lost completely (clonal deletion) the specific types of T-lymphocytes needed for

defense against the leprosy bacillus. Others suggest that these cells are not lacking but may have been "turned off" either by the presence of too much antigen or by the action of other immunoregulatory cells i.e. "suppressor cells", that may have been powerfully stimulated to suppress normal T-lymphocyte or macrophage function in the face of chronic active infection.

Additional perturbations of immune function have been observed among lepromatous patients and/or in experimental models of leprosy that may contribute to the dysfunction of CMI. These include the presence of circulating humoral factors that are inhibitory to T-lymphocyte function and elevated serum levels of a chemotactic inactivator. The latter directly inactivates various chemotactic factors that appear to be important in attracting different types of leukocytic cells to a site of infection or foreign protein (antigen) deposition. Still another mechanism by which the immune responses of lepromatous patients may be impaired relates to possible disturbances in the traffic of T-lymphocytes. T-lymphocytes normally recirculate continuously through the body from the blood through lymph nodes and thence back to blood via the thoracic duct. T-cells also recirculate through the spleen. This extensive trafficking of T-lymphocytes is believed to serve an important role in bringing immunocompetent cells to local areas containing foreign (antigenic) materials or infection. Recirculation therefore allows specifically sensitized cells within the body to reach a particular trouble spot. Here, they multiply and attract other cells especially those of the monocyte-macrophage series to join in the attack upon foreign material. In experimental animals with severe mycobacterial infection resembling lepromatous leprosy, there is marked disruption of the normal lymphocyte recirculation secondary to extensive trapping within the spleen and lymph nodes (5). This type of cell traffic disturbance may also occur in humans and could interfere with the proper function of CMI.

II. IMMUNOTHERAPEUTIC AGENTS

A. BCG and *Corynebacterium parvum*

Despite our incomplete understanding of the multi-factorial disturbances of immune function associated with leprosy, an era of immunotherapy has begun and pilot studies with several approaches have been initiated or are in planning stages. The first type of immunotherapy to be considered seriously for lepromatous leprosy was the use of an immunological adjuvant.

During the 1950's, several workers confirmed the fact that vaccination of lepromatous patients with the bacillus Calmette-Guerin (BCG) could convert the Mitsuda skin test from negative to positive in up to 50% of cases. Furthermore, the histological appearance of the skin reaction to lepromin injection is frequently improved after BCG ; the granulomatous reaction often bears tuberculoid features of increased lymphocyte infiltration and giant cell formation. These features are not found in biopsies of lepromin test sites taken prior to BCG vaccination. Skin test reactivity to lepromin after either one or two vaccinations with BCG does not persist and reverts to negative in less than five months in most cases.

The waning of lepromin reactivity plus a lack of demonstrable clinical improvement in lepromatous patients after BCG vaccination led to abandonment of this approach. However, an important series of observations by Dr. George Mackaness and his co-workers during the 1960's has led to a renaissance of interest in BCG as an immunopotentiating agent. These workers determined that induction of a cell-mediated immune response in experimental animals to a specific pathogen, for example, *Listeria monocytogenes*, also caused a transient increase in resistance to infection by *other* facultative intracellular micro-organisms such as *Salmonella enteritidis*. Rechallenge of animals recovered from *Listeria* infection with a second injection of *Listeria* resulted in more rapid destruction of organisms as the result of a specific CMI reaction. If animals recovered from the primary *Listeria* infection were challenged subsequently with *S enteritidis*, elimination of these organisms was not accelerated. Conversely, if animals with previous *Listeria* infection were rechallenged simultaneously with *Listeria and S. enteritidis* then the elimination of both organisms was accelerated.

These findings indicate that during an active cell-mediated immune response to a *specific* infecting organism, there is concurrent stimulation of a more generalized cellular immune response that can act non-specifically against pathogens of *different* species. The cell ultimately responsible for destruction of micro-organisms in experiments described above is

the macrophage. In states of heightened CMI, the macrophage is "activated" to increased phagocytic, bactericidal and cytotoxic activity by mediator substances called "lymphokines" that are released from sensitized T-lymphocytes after contact with a specific antigen.

In human disease, efforts to boost the non-specific component of CMI have been most extensive in the field of oncology. By giving repeated injections of living BCG to certain cancer patients, it is hoped that there will be sufficient non-specific stimulation of macrophage cytotoxicity to kill malignant cells (6). At least in theory, it seems reasonable to approach generalized intracellular infections in a similar fashion. Thus, if a strong cell-mediated immune response to BCG could be induced repeatedly in patients whose macrophages are ineffectual against an intracellular pathogen, then it may be possible to increase killing of this pathogen secondary to the non-specific macrophage activating effects of BCG. Of interest is one reported study in which lepromatous patients with a low Bacterial Index after years of sulfone treatment were given an intradermal injection of killed *M. leprae* (7). *M. leprae* were cleared very poorly from the injection site during an observation period of 30 days. However, if the same number of *M. leprae* were admixed with BCG organisms or other mycobacteria and injected into another site, the local deposit of leprosy bacilli was cleared by a granulomatous reaction containing lymphocytes, epithelioid cells, and some giant cells. Though unconfirmed, this report provides an additional stimulus for controlled studies to assess the immunotherapeutic effects of giving BCG repeatedly by scarification over several months.

A priori, it seems that patients capable of converting their tuberculin skin tests to positive after BCG vaccination might stand a better chance of reducing a large load of leprosy bacilli through BCG induced T-lymphocyte stimulation of macrophage activity than those who do not. Unfortunately, cell-mediated immune function may be depressed non-specifically in significant numbers of patients with advanced lepromatous leprosy. Thus, the probability of converting these patients to tuberculin positivity may be diminished. On the positive side, however, it appears that the non-specific depression of CMI is frequently reversible after a year or more of effective anti-leprosy chemotherapy (8). Intensive BCG therapy therefore may hold more promise as a means for augmenting chemotherapy at a time when the bacterial load has been reduced considerably. By propitious timing of immunotherapy it may be possible to destroy the population of microbial persistors that appear to be responsible for many of the relapses observed after cessation of conventional chemotherapy.

It must be emphasized that intensive BCG therapy is not without hazards. Systemic reactions to this type of treatment consist of fever, chills, anorexia, and myalgias. These occur within four to six hours after injection and generally subside within 36 to 48 hours but may last longer. Hepatic dysfunction with jaundice, granulomatous hepatitis, and disseminated BCG infection have been reported (7). In leprosy patients there is the added hazard that if BCG should augment CMI to *M. leprae*, nerve damage might ensue subsequent to activation of the inflammatory response within nerve lesions. Likewise episodes of erythema nodosum leprosum (ENL) may be triggered. These concerns of course apply to *any* type of immunostimulatory therapy that may be attempted in leprosy patients.

Because of problems encountered with living BCG in tumor immunotherapy, many treatment centers are now utilizing the adjuvant properties of another organism, *Corynebacterium parvum* for immunotherapy. This organism can be given intravenously in killed form and has been better tolerated in man and experimental animals. Whether *C. parvum* therapy will produce acceptable clinical results has not yet been fully determined. Above all, it must be remembered that one is brandishing a two-edged sword when treating intensively with *C. parvum* or BCG. Without doubt, immune responses can be stimulated by appropriate dosages of either adjuvant, however there is also clear evidence that administration of BCG or *C. parvum* may actually depress cellular immune function in some cases. The mechanism by which these agents may depress CMI is unclear but there is some evidence to suggest that with intensive antigenic stimulation of this type, homeostatic control mechanisms may be activated to gnerate suppressor cell populations which act to dampen the CMI response.

B. Drug Therapy

Currently there is some enthusiasm for therapeutic trails of the chemically defined

compound levamisole (Katarax[R]) to augment the immune response. This antihelminthic drug given in a dosage of 150 mg per day for three days has been shown to restore cutaneous delayed hypersensitivity in some anergic patients with cancer (9). *In vitro*, levamisole has been found to increase the percentage of T-cell rosette formation* by lymphocytes obtained from normals and patients with Hodgkin's Disease. The action of levamisole is complex and not entirely understood. However, because T-lymphocyte function as well as that of macrophages may be improved by its action, levamisole is undergoing evaluation as an immunopotentiating agent in the treatment of cancer.

The rationale for a similar trial of this drug in leprosy is obvious, and studies are underway in several countries. In one well-controlled study, levamisole treatment was found not to increase the intensity of Fernandez or Mitsuda reactions in lepromatous patients (10). It might be said in passing that the author has attempted to treat rats heavily infected with *M. lepraemurium* using levamimisole for long periods but no significant reduction in bacillary load or in mortality was achieved. Although levamisole appears to be a reasonably safe drug, severe side effects have been reported in cancer patients. These include central nervous system disturbances, severe skin rashes, reversible agranulocytosis and a flu-like syndrome (11).

C. Thymic Hormones

The thymus is necessary for normal differentiation and maturation of T-cells that are fundamental to the expression of CMI. One way the thymus effects the maturation of T-lymphocytes is through the secretion of hormones. The first of these was discovered about eleven years ago by Drs. Allan Goldstein and Abraham White who called it "thymosin". Thymosin is a partially purified preparation obtainable from the thymus glands of a number of animals and its effects are not species specific. The mechanism of thymosin's action is not completely understood however it appears to convert immature T-cells into mature forms that are immunologically competent. In certain cases of congenital thymic dysfunction frequent administration of thymosin can maintain T-cell count in peripheral blood at near normal levels and can correct some but not all of the deficient immune functions (12).

Patients with cancer frequently suffer from deficiencies of CMI, and the absolute number of T-lymphocytes (SRBC-rosetting cells) in their peripheral blood may be low. *In vitro*, addition of thymosin to blood lymphocytes from some of these patients produces a rapid increase in the number of rosetting cells. Because of the above findings, a major study is underway in the United States to determine the safety of thymosin therapy and to learn what benefit, if any, it may provide to patients with cancer and certain immunodeficiency diseases.

There is also justification for carefully controlled studies to determine if thymosin or other thymic hormones might prove beneficial to patients with lepromatous leprosy, especially to those in whom the absolute number of blood T-lymphocytes is abnormally low (13). The desirability of a thymosin trial in leprosy patients is underscored by a recent report that the inexorable progression of an experimental infection with viable BCG in T-cell depleted mice can be prevented by intensive thymosin therapy of the immuno-depressed animals (14).

D. Lymphocyte and Transfer Factor Therapy

Over twenty years ago, H. Sherwood Lawrence and associates determined that, in humans, viable blood leukocytes are effective in the transfer of delayed cutaneous sensitivity to tuberculin and to streptococcal antigens. Subsequently, Dr. Lawrence found that extracts of human leukocytes obtained by freezing and thawing or by osmotic lysis were as effective as intact viable cells in transfering systemic states of delayed hypersensitivity that persisted up to two or three years. This active material he called transfer factor (TF). Although it is now known that TF is a product of lymphocytes, the nature of this product has not been fully determined. For this discussion it will suffice to mention that TF is a soluble, dialyzable material with a molecular weight of less than 10,000 that can be freeze-dried to retain potency for at least five years. TF does not induce antibody formation against itself in the recipient even after repeated injections.

*Non-specific, spontaneous formation of rosettes with sheep red blood cells by lymphocytes is a commonly used marker for the T-cell sub-population in humans.

Transfer factor was poorly received by the scientific community for many years because it was not possible to demonstrate the transfer phenomenon in any animal but man and because evidence for activity was restricted to the reading of skin tests only. Nevertheless, clinicians were attracted to the idea that TF might be of benefit in treating immunodeficiency disorders or patients who fail to mount an adequate cell mediated response to serious infections with intracellular pathogens.

In 1968, the author began studies of TF therapy in leprosy (15). During these studies, Paradisi et al. reported successful conversion of the Fernandez reaction to positive in four of 13 lepromatous patients to whom they had given approximately 2×10^6 viable leukocytes from donors who were sensitive to lepromin (16). Subsequently, we observed conversion from anergy (lack of skin reactivity) to weak skin test positivity to *M. leprae* (Dharmendra preparation) in six of nine patients given 4.1×10^8 lymphocytes or TF from equivalent cell numbers donated by individuals reactive to *M. leprae*. In six patients, positive skin reactions were elicited at test sites remote from the injection of TF or cells indicating that a state of systemic hypersensitivity had been induced. In a seventh patient, a positive skin test was induced only locally at the site of TF injection. No long term clinical benefit resulted from the TF or cell injection. Nevertheless, five patients experienced significant inflammatory changes within their skin lesions that were characterized by increased erythema and induration. In two of three cases from whom skin biopsies were obtained before and after administration of TF, there was an influx of lymphocytes in the post TF specimen. These "flare" reactions were of short duration (seven to 12 days). However, they were very similar to the more permanent reversal reacactions that arise spontaneously in some patients after prolonged antibiotic therapy and are regarded as a harbinger of clinical improvement.

Silva et al. failed to transfer sensitivity to *M. leprae* with TF or ribonucleic acid from lymphocytes of skin test positive donors although reactivity to other antigens was transferred successfully in some cases (17). Antia and Khanolkar treated each of seven lepromatous patients with 1.2×10^8 lymph node cells from a lepromin positive donor (18). Neither the Fernandez nor the Mitsuda test was converted to positive although substantial increases in the lymphocyte response (blast transformation) to lepromin were observed in two cases 48 hours after cell transfer. Conversely, Mendes et al. were successful in transferring lepromin sensitivity (positive Fernandez and Mitsuda reactions) to three of seven lepromatous patients by giving viable leukocytes from sensitive donors (19). Using a single injection of TF prepared from patients with tuberculoid leprosy, Han and Weiser converted three of four lepromatous patients to cutaneous reactivity against lepromin (Wieiser, R. R., personal communication).

Recently, Hastings et al. have employed multiple doses of TF given three times weekly for twelve weeks (one dose equivalent to 2×10^8 lymphocytes) to treat three patients with advanced lepromatous disease (20). Each patient developed the "flare reactions" previously described. These reactions persisted throughout the course of TF therapy and abated when treatment was discontinued. Biopsies of the reactional skin areas revealed an influx of lymphocytes within the granulomata and the rate of fall in the Bacterial Index was accelerated. Unfortunately, the accelerated fall in Bacterial Index did not persist after discontinuing TF. Furthermore, TF did not significantly reduce the percentage of dermis involved by granulomata.

These findings are intriguing, especially the ability to induce transient "flare reactions" and skin test conversion to Dharmendra lepromin. On balance, the preliminary evidence suggests that reduction of the antigenic load by intensive chemotherapy followed by repeated doses of transfer factor may prove to be an effective means of helping patients to gain and maintain a more effective immune response against *M. leprae*. The need for reduction of antigenic load and repeated TF administration is underscored by reports of dramatic but very temporary improvement (three to five months) in patients with another chronic infection known as muco-cutaneous candidiosis who are given single doses of TF. However, if the antigenic load provided by chronic infection with *Candida albicans* is first reduced by amphotericin B therapy, repeated administration of TF may be successful in maintaining prolonged remissions. Together with the somewhat encouraging results of studies on TF therapy for systemic coccidioidomycosis, a serious mycotic infection, the preliminary experience in leprosy suggests the time is at hand for conduct of well-controlled double-blind studies on the value of intensive

TF therapy in leprosy and other serious intracellular infections.

The cumulative experience with TF therapy is considerable yet very few adverse effects have been reported. Serious complications have been reported after TF therapy in two isolated cases, each involving a different type of congenital immunodeficiency (21,22). The first patient developed an autoimmune hemolytic anemia after multiple doses of TF. In the second, there was an uncontrolled proliferation of antibody producing lymphocytes (B-cells) after TF. It is uncertain whether these complications were actually caused by TF since patients with either type of immunodeficiency are prone to spontaneous occurrence of the disorders described. Perhaps the side effect of TF to be most feared in leprosy would be activation of an acute, disabling neuritis and/or ENL as a result of the improved inflammatory response to *M. leprae.* In the very limited experience to date, increased nerve dysfunction has not been a significant problem during TF therapy, but ENL of modest severity may be precipitated. In addition, fever, increased nasal congestion, lymphadenopathy, arthralgias and atypical lymphocytes in peripheral blood have been observed in association with TF therapy of leprosy patients (15).

Two major questions regarding TF are unresolved. First, it is not known if TF acts specifically by transferring immuno-reactivity only to antigens that have sensitized the cell donor or if it acts non-specifically as a type of immunological booster or adjuvant. The issue is of considerable practical as well as theoretical importance for if TF does prove to be a reasonable therapeutic agent and its action *is* nonspecific, then the supply of useful TF would be greatly expanded through use of frozen blood bank leukocytes from normal donors. In addition, cost, a major consideration in the therapy of leprosy, would be greatly reduced if blood bank leukocytes could be used. The second unresolved question is how TF works. Hopefully, answers should be forthcoming within the reasonably near future since techniques are now available for studying the activity of TF on isolated cell populations in the test tube. Furthermore transfer factor-like activity has been found in the leukocyte extracts from several animal species and these substances are under intensive investigation in parallel with human TF.

E. Massive Infusions of Allogeneic Cells

In 1972 Lim et al. published the results of a therapeutic endeavor in which leprosy patients were given massive intravenous infusions of peripheral blood leukocytes from unrelated donors who apparently were normal (23). The patients received as many as ten weekly infusions, each containing more than 1×10^9 cells. In three cases of lepromatous leprosy the authors claim to have observed dramatic improvement with 1) disappearance of the myriads of acid-fast bacilli in lymph nodes and skin, 2) substantial replacement of foamy macrophages (Virchow cells) within diseased lymph nodes by sheets of normal appearing lymphocytes and 3) cessation of ENL reactions to chemotherapeutic drugs. All of these changes are said to have occurred within 13 weeks after the inauguration of leukocyte transfusions. To date, these claims have not been confirmed by other investigators and the authors have provided no long-term follow-up of the original study.

Saha et al. treated five patients with somewhat smaller numbers of allogeneic* cells and noted a decrease in ENL activity in two of the three lepromatous patients (24). One patient with borderline lepromatous and one with tuberculoid leprosy who had developed "severe reactions" to DDS became more tolerant to the drug during and shortly after the period of leukocyte infusions. Bacteriological and histological improvement was observed after five months in two of the three lepromatous patients. Of these two, the patient showing greatest improvement was also treated with unknown quantities of DDS.

The dramatic report of Lim et al. and that of Saha et al. provoke speculation as to just how infusion of allogeneic cells in large numbers might benefit leprosy patients. First, it is possible that the infused lymphocytes themselves were able to survive long enough to mount an immune response before being killed by the recipient. Alternatively, if the infused cells were promptly killed, a considerable quantity of TF and/or lymphokines may have been released to stimulate the recipient's own immune cells. A more probable explanation is that allogeneic lymphocytes within the infusions reacted against immune cells of the recipient in such a way as to actually stimulate a non-specific increase in the immune response to antigens of *M. leprae.* This so-called "allogeneic effect" has been well described in animals and has been shown to increase resistance to infection with intra-

* The terms "allogeneic" in this case denotes leukocytes that are of the same species but antigenically unrelated.

cellular pathogens such as *L. monocytogenes* or *Salmonella typhimurium* (25). The mechanims by which a graft versus host reaction can stimulate the host's immune function is complex in that it may potentiate the function of B-cells, T-cells, and macrophages as well (26).

As attractive as the concept of a dramatic reversal in the clinical course of lepromatous leprosy may be, the administration of massive allogeneic cell infusions to leprosy patients is fraught with serious ethical and practical considerations. Unlike TF therapy, massive infusions of leukocytes from different donors is certain to transmit type B hepatitis in significant numbers of cases. Although acquisition of hepatitis can be diminished by rigid screening of donors for HB_s antigenemia, hepatitis transmission will still occur. The prospect of infecting lepromatous patients with type B hepatitis virus is of special concern since some studies have reported an increased prevalence of chronic HB_s antigenemia among these individuals possibly as a consequence of the non-specific depression of CMI often associated with lepromatous disease (27). In addition, recipients of leukocytes will be subjected to the risk of acquiring other infectious diseases especially those caused by latent viruses such as *Herpes* and *Cytomegalovirus*.

Another major concern is the possibility that large numbers of infused lymphocytes may mount a graft versus host reaction far in excess of that required to augment host cell reactivity. Severe graft versus host reactions are frequently encountered in severely immunosuppressed patients who lack competent immune cells to fight back and destroy the invading donor cells. The clinical picture is typically one of severe skin rash, hepatic dysfunction, intestinal involvement with diarrhea and further depression of the host's already limited immune function (28). Death is common unless the invading cells are destroyed or a state of chimerism can be achieved. Lim did not observe dangerous graft versus host reactions among his patients probably because the non-specific impairment of CMI in lepromatous leprosy is much less severe than encountered in congenital immunodeficiency diseases or among patients undergoing intensive immunosuppressive therapy. Nevertheless, the risk is real of inducing a harmful graft versus host reaction in patients with lepromatous leprosy and cannot be dismissed especially in those who have been treated chronically with substantial doses of steroids for ENL.

III. CONCLUSIONS

In conclusion it can be said that the long range outlook is fairly good for development of effective immunotherapeutic approaches to leprosy. Immunotherapy may prove quite valuable in reducing the rates of relapse caused by *M. leprae* that are capable of surviving as persistors throughout long courses of chemotherapy. Current approaches to the immunotherapy of leprosy are far in advance of what we actually know about the complex mechaninisms of immunity to this chronic intracellular infection. Therefore, tomorrow's approaches may well differ considerably from those of today.

A hint of new approaches to immunotherapy that may be yet to come is provided by the rapidly expanding knowledge of feedback suppressor mechanisms in animals and man. These suppressor mechanisms function to control the immune responses so that they do not continually over-respond to the barrage of immunostimulants present in our environment. Many of the suppressor control functions are mediated by a sub-population of T-lymphocytes commonly called "suppressor T-cells". Already, there is evidence in man that chronic intracellular infections can be associated with *excessive* T-cell suppressor activity (29). Whether the excess suppressor activity may contribute to the disease chronicity and to the generally poor cell-mediated immune responses of these patients remains to be seen.

In our laboratory we have observed powerful suppressor cell activity in experimental mice infected with *M. lepraemurium* (30). Actually we have detected two separate suppressor cell populations that are active in infected animals. The first is composed of macrophage-like cells that are activated to suppressor activity during early infection. These cells continue to act as suppressors throughout the course of infection until death. The second population of suppressor cells consists of T-cells that become very active after the tenth week of infection. Currently, we and others are studying humans with disseminated intracellular infections to define the nature and extent of suppressor cell activity. Should "overstimulation" of suppressor cell activity be detected in these patients and proved to be of functional significance, it

is clear that the thrust of experimental immunotherapy may be altered considerably.

The newer immunotherapeutic agents are capable of causing harm as pointed out above. Therefore the use of these agents must be implemented with caution and with reference to the best available knowledge of human immunobiology. Double-blind control techniques must be employed wherever possible. Last but not least, sophisticated facilities must be available for treating the unexpected complications of immunotherapy in volunteers who have been carefully educated so that they are capable of giving truly informed and voluntary consent to the procedures of medical exploration.

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TOTAL POPULATION SURVEY OR INTENSIVE HEALTH EDUCATION?

DR V EKAMBARAM

Introduction

Good health is an essential requisite for any human being to lead a happy life and hence our ancients have given the science of medicine (AYURVEDA) the status of a veda. The first sign or symptom of ill-health that causes any person to seek the advice of a physician is noted first by the patient himself and so, to a certain extent, varying from person to person, everybody knows what is abnormal about one's health. It is also imperative that this awareness should be increased and educated in a scientific manner. This is true of all diseases that cause acute bodily suffering, but then, in certain diseases like leprosy, in which, in the early stage of the disease, the bodily suffering is very little or nil, recognition of the abnormality of health is missed. Combined with this, the common optimism that such diseases causing no acute suffering are not serious, delays the recognition of the disease till such a stage when the disease becomes too advanced to be ignored. This is the crux of the situation with reference to leprosy. Hence it is the aim of this paper to analyse how far the creation of an awareness of the signs and symptoms of this disease in the general public can lead to the recognition of the disease by themselves instead of waiting till the same is detected by trained health workers.

National Leprosy Control Programme and case-detection

In the 3 principles of the National Leprosy Control Programme, case-detection is the first one. The age-long belief that leprosy means hideous deformities delays the recognition of the disease till deformities develop. This has resulted in the disease not being recognised at the early stages when the manifestations consist of patches on the skin. This has made the recognition of the disease difficult by the public at large and even those few, who could recognise the disease early, fail to report for treatment on account of the stigma attached to the disease. This has resulted in the necessity for a survey, by trained workers of either total population or a sample of the population. But, in general, in the areas of the control units, where the public have not been taught about the early signs and symptoms of the disease, very few recognise the disease unless survey of the population is done by trained health workers. Hence it is obvious that survey of a population for leprosy is only necessitated by lack of proper health education of the community about leprosy.

Let me discuss the methodology of survey and the merits and demerits of survey for case-detection work.

Intensive survey

Every modern control unit is divided into 20 sub-centres and a para-medical worker is incharge of the intensive control work in his sub-centre, which includes survey.

The population of a sub-centre is about 20,000 and the paramedical worker can devote about 3 days in a week for survey. So, to complete the survey in a sub-centre, the para-medical worker takes about 2 to 3 years, if he has to do it by himself (though in a few States, team survey is being done, e.g., Maharashtra). Hence for one survey to be completed, it takes a few years and quite a lot of changes (origin of new cases, deaths and migration of old cases, immigration of new cases) would have happened in the interval and so the survey *findings are vitiated.* In addition most of the para-medical workers

are young, inexperienced persons, who are unable to command the respect and co-operation of the villagers and so the survey is done with great difficulty and so in an imperfect manner. Of course, it is ordered that the survey in a village should be preceded by a health education meeting carried out by the Medical Officer so that the survey work is made easy for the paramedical worker. But this is very rarely done and hence the survey is imperfect. Besides all these, since the majority—if not all the para-medical workers are males, the examination of women is very cursory and so quite a few cases are missed. This is specially so in areas populated by muslims, where '*purda*' is observed. Besides all these difficulties faced by the para-medical worker, there is the difficulty of even frank hostility from the public for survey for leprosy. It is the experience of many a para-medical worker—even of a senior worker—to come across families, who absolutely refuse to be examined, specially for leprosy. This is made worse by too many workers visiting the villages, for various vertical programmes. In short the carrying out of survey, by a para-medical worker is so difficult that one wonders if it is worth all the energy spent on it (the time and money). In addition, quite a few para-medical workers are careless in their work. Some are even dishonest and hence the survey findings are not worth taking into account except in very few centres.

But then, the basic aim of survey is not merely detecting patients but also to study the epidemiological aspects and to induce patients to come for treatment. The experience in this direction till now has been rather disappointing since the survey is done of an unwilling public and a public, who rarely believe the findings of a para-medical worker with the result that quite a good number of such patients—except in few centres—do not turn up for treatment and so all the energy spent on survey is wasted. Due to the difficulties experienced in survey enumerated above, the % of population examined in the so called total population survey is low i.e., about 80% with the result that quite a few cases are missed and so, such a survey is not worth the energy spent on doing it.

In short, since survey is something forced on a public that are generally not aware of its significance, since in the majority of the areas where survey is done, the public are not prepared for this and since there is always a reluctance to be identified as suffering from leprosy, except in very few areas where intensive health education has been done prior to survey, the survey findings are not as useful as one would expect commissurate with the time and energy spent on it.

In this connection, it is relevant to quote from the report on "Leprosy Control, Pogiri, Srikakulam, Andhra Pradesh, India, Jan., 1962—December, 1966", the views expressed about case-detection by mass survey in comparison to case-detection by health education supplemented by contact survey and school survey.

"Analysis of standard methods of case-finding

In order to assess how far the above-mentioned methods of case-finding had been successful in achieving the aim of satisfactory coverage of all the existing cases in the population, a coverage study was carried out in August, 1964. In the six control units first established, a mass survey was carried out two years after the start of the work in which the whole population of 98,425 was registered. In house-to-house examinations, it was possible to examine, by a special team of experienced leprosy auxilliary workers only 60% of those who had not yet been examined in contact surveys or school surveys or were not registered for treatment. A 10% sample survey among the 40% absentees at the time of this house-to-house survey revealed that the rate of leprosy prevalence among them corresponded to the prevalence rate in the group examined. In this way, a picture of the leprosy pattern of this area could be formed. From the estimated 4,652 existing cases (660 lepromatous), 62% had come forward voluntarily, 7% were detected in the contact survey and 9% found in the school survey. The mass survey added to this figure only 13%, leaving 9% undetected. For the lepromatous cases this coverage was even more striking: 89% voluntary, 3% contact survey, 0.3% school survey, making total of 92.3%. The mass survey could add to this only 5% with a remaining 3% still undetected.

The mass survey added, in fact, only a little to the known case-load. The fact that over 90% of the lepromatous cases and 75% of the non-lepromatous cases had not only been detected but also brougnt under treatment through the standard methods, is highly satisfactory. In this connection, it may be mentioned that an analysis of treatment regularity in 1965 showed that from the cases

detected in the mass survey in that year, only 25% belonged to the group of regular attenders (i.e., attending over 75% of the treatment sessions) compared with 50% of the cases detected in the contact survey and 74% of all the cases detected during that year.

Furthermore, it may be added that in five of the six control units in which this study was performed, the mass survey was repeated in 1966, after two years. In these five units, with a population of 75,177 and a prevalence rate, after the first mass survey, of 26.3 per mille, the standard methods of detection added 13.7 per mille and the second mass survey only 1.3 per mille to the prevalence rate. This strongly suggests that the previously undetected cases have now been detected by means of the standard methods, especially since the mass survey revealed only early cases".

CONCLUSION:

The data presented in this paper amply proves that it is better to utilise health education for case detection than carry out surveys of an unwilling and unprepared public. It is also evident that those who are able to detect the disease in themselves by themselves as a result of health education are also better motivated to be regular for treatment. But then, the important part of this method of case-detection is to do effective health education which is suitable to the public for whom it is meant. Merely adopting conventional methods of health education in a traditional manner may not be effective and hence one has to carefully and intelligently plan the methods of health education so that it could achieve the desired results. In addition, the ultimate goal for the control of all communicable diseases should be to involve the community as a whole in the implementation of such schemes.

Case-detection by survey compared with Health Education, contact survey etc.

A similar analysis of the data on this aspect of the work of our project i.e., the No. of patients detected by intensive survey and the No. detected by other methods, is presented in the Table No. I, given below.

TABLE No. I

Total New cases detected in a period of 1970 to 1976

Year	Total No. of cases detected				SOURCE OF DETECTION															
					By survey				By examination of healthy contacts				By patients reporting voluntarily for treatment				During routine village visits			
	L	N	N?L	Total	L	N	N?L	Total	L	N	N?L	Total	L	N	N?L	Total	L	N	N?L	Tol.
1970	375	6164	304	6843	83	2023	67	2173	—	185	—	185	278	3803	227	4308	14	153	10	177
1971	161	3166	104	3431	31	1336	19	1386	6	287	4	297	117	1471	80	1668	7	72	1	80
1972	88	2113	97	2298	24	946	17	987	2	207	6	215	61	932	71	1064	1	28	3	32
1973	159	2192	114	2465	40	986	24	1050	1	191	10	202	115	976	79	1170	3	39	1	43
1974	65	1562	70	1697	19	751	13	783	2	160	4	166	43	631	49	723	1	20	4	25
1975	77	1851	147	2075	35	1095	50	1180	2	190	9	201	39	555	84	678	1	11	4	16
1976	61	1774	278	2113	29	1098	131	1258	4	237	21	262	28	434	123	585	—	5	3	8
Total	986	18822	1114	20922	261	8235	321	8817	17	1457	54	1528	681	8802	713	10196	27	328	26	381

COMMENTS:—It is seen from Table No. 1 that out of a total of 20,922 patients detected in a period of 7 years, the No. of patients detected by intensive survey is only 8,817 whereas 12,105 have been detected by methods other than survey. The No. who reported voluntarily for treatment, probably as the result of health education is 10,196 out of a total of 12,105 detected by methods other than survey. This itself proves that case detection is better achieved by health education supplemented by contact survey, school survey, etc.

Attendance requalarity of patients detected by intensive survey and of those voluntarily reported for treatment :

The analysis of the regularity of patients for treatment detected by intensive survey and of those voluntarily reporting is given below in Table No. 2 (Regular—being defined as those who attended for 50% and more of the clinic days).

TABLE No. II

Years of detection	No. detected by intensive survey				No. of patients who took regular treatment i.e., (50% and more of the clinic days)				No. detected by voluntarily reporting for treatment				No. of patients who took regular treatment (i.e., 50% and more of the clinic days)			
	L	N	N?L	Total	L	N	N?L	Total	L	N	N?L	Total	L	N	N?L	Total
1974	—	60	2	62	—	44	2	46	3	51	6	60	2	43	6	51
1975	1	63	6	70	1	51	6	58	5	62	12	79	5	59	11	75
1976	6	132	26	164	5	106	24	135	4	45	19	68	4	43	17	64

COMMENTS:—It is seen from the data in Table No. II that the regularity of patients for treatment of those voluntarily reported for treatment is much better than those detected by survey in a 3 year period for obvious reasons.

It is obvious from the data presented above that whenever a patient is intelligent enough and also leprosy conscious to observe early signs, suspicious of leprosy, he is also motivated to take treatment regularly, unless of course, the medical man treating him is grossly careless or indifferent in treating such a patient. But on the contrary, those persons, in whom the disease had to be detected by another person—trained health worker—is not convinced about the diagnosis or lacks the initative to come and take treatment regularly. Hence it is evident that our effort should be to make the individual citizen take interest in his health and come to us in the early stage of the disease by intensive and effective health education. As a matter of fact, it would be much better if the community as a whole is not only given health education about such diseases, but also motivated to take the leadership for working control schemes of communicable diseases reminding us of what an elder Statesman said about the role of generals in war—"War is too serious a business to be left to soldiers completely". Hence I am firmly of the opinion that intense health education and motivation of the public to take social leadership for the control of communicable diseases which should be a part of integrated rural development is the only solution to the problem of leprosy as well as other communicable diseases. But it could be better to assess the efficiency of such a method of case detection by health education—supplemented by contact survey, school survey etc. by checking it with random sample surveys in the area.

A CRITICAL LOOK AT SOCIETY'S HEALTH EDUCATION IN LEPROSY

M. S. MEHENDALE

Contents

Introduction

Some result oriented scientists and social workers are now getting impatient or disappointed. They feel that our leprosy control programme is not going in the correct direction. Their anxiety is quite genuine and understandable. This is because leprosy patients are still victimised. They suffer privations, boycott and the like. The common man is still afraid of leprosy.

In the first stage of the planning and initiation of leprosy control work, hopes were high. We were told that if the Survey Education Treatment programme were implemented, we would be able to control leprosy within a foreseeable future. Though no one was able or willing to commit by a time bar, it was hoped, presumed and believed that we would control leprosy, say in 25-50 years. Do we estimate the same way now? Despite decades of leprosy control work we have not yet been able to categorically say whether leprosy has been on the increase or decrease. Have we controlled the disease at least in those areas where work has been going on for a long time? Answers to such queries are vague and non-committal. In reality we do not know the answers and what we can do is to make a 'considered guess' instead of saying yes or no. Such considered guess may be understood and appreciated by the top level people but for the lay persons it means nothing.

Explanations of such situations may be many.

One of the ways to explain our failures is that the Survey Education Treatment pattern has never been implemented with necessary weightage to all its components. Health Education for instance, has always been the subject of studied neglect by the high-brows who plan, or lowly technicians who implement it. It is only recently realised on an increasing scale that proper and adequate health education of the people is absolutely necessary for the successful implementation of our plans.

It must be clearly understood that mere

health education, howsoever effectively conducted, will not be the only or the final solution. Health education by itself will be useless unless it is supported by solid, efficient service to the patients. Many enthusiastic advocates of health education tend to forget this.

The need for health education in leprosy

Health education of the common man with respect to leprosy becomes imperative on account of the main causes mentioned below:—

1. Trouble-free and insidious onset of the disease.
2. Misunderstandings, superstitions, fear, wrong notions, etc. that prevail in the society with respect to leprosy.
3. The availability of potent modern drugs which cure leprosy, no matter whatever the stage or the type of the disease.
4. Lack of preventive vaccine or inoculation to primarily protect the population from leprosy.

Before going into the details of the above reasons, it must first be clearly understood that these reasons do not apply exclusively in case of leprosy. Vaccines are not available for many diseases. Many diseases start in a trouble-free and insidious manner. Misunderstandings, etc. prevail about every health matter. Modern drugs are available for many diseases, previously taken as incurable.

In leprosy, the depth, intensity and widespread prevalence of these is perhaps more than that in others. Is addition the deep-rooted social connotations attached to leprosy are not seen in other conditions.

Let us now see these reasons more closely.

1. Trouble-free early signs

The anaesthetic patch or change in the colour and texture of the skin, which are the early signs in leprosy cause no physical discomfort to the patient. There is neither itching, nor pain nor burning at the site of the changes. They can be misleading.

When any disease starts in a trouble-free and insidious manner it leads to two serious consequences. Thus, if such trouble-free signs appear on the parts of the body one does not see, the person may be totally unaware of the disease. Again even if such signs appear on the part of the body one can see, the person concerned ignores them because they cause him no trouble.

Another reason for not going to the doctor in the early stages of the disease is the non-association of the early signs with *leprosy*. The common man feels that leprosy means deformity. He has this idea fixed in his mind. He cannot even imagine, therefore, that the signs that have appeared on his body could be on account of *leprosy*.

In all these cases, therefore, the net result is that the disease remains undetected and unattended for a considerable time.

2. Misunderstandings, wrong notions, superstitions, etc.

Every matter regarding health has some or the other wrong notion about it, may it be baldness or gray hair, diet, cold, fever or the rest. Ignorance about scientific facts is the breeding ground for these superstitions and misunderstandings. In case of leprosy as compared to other diseases scientific progress remained very slow and meagre. Hence the wrong notions, misunderstandings, etc. are deep rooted. They are observed in every society of the world and each and every class of every society. As a result, leprosy is feared, it becomes a dangerous disease in the eyes of the common man. The society and the patient are mutually afraid of each other. There is tendency to hide the disease on the part of the patient and tendency to boycott or avoid the patient on the part of the society.

3. The availability of modern drugs

This is the most important reason why health education of the society should be done on a large scale. For a long time no drug that would cure leprosy was known. Leprosy was taken as an incurable disease. But now we have drugs which cure leprosy irrespective of the stage or type of the disease. The commonest drug is simple and cheap. It is freely available. The treatment is simple to administer because it is available in the form of tablets. If a patient tolerates the drug, supply adequate for a month or more can be given to him with instructions about taking it daily. He need not report daily to the doctor.

In addition, we also have several other potent drugs, second line drugs, for the treatment of leprosy. True, some of these drugs are costly. But with their availability, the

problem of treatment of leprosy cases is much more easy. There is good hope of saving a patient from becoming a total liability.

Several advantages are seen if treatment is started when the disease is in the early stages. Thus, a patient does not lose his job or home, he gets cured earlier, his infectivity, if any, is rapidly reduced rendering him non-infectious. Deformity is avoided and thereby all problems consequent to it such as dehabilitation and the need for rehabilitation are also avoided.

With such a powerful weapon in our hands it would be a pity if patients remain without treatment for long time, develop deformity and eventually lose home, jobs, positions in the society, etc. and resort to begging.

4. Lack of preventive vaccine/inoculation

This means the sure and simple method of primary prevention available in many diseases such as small pox, tetanus, poliomyetitis etc. is not at hand in case of leprosy. This also means one has to wait till the disease actually starts. Nothing can be done to prevent this.

Let us now discuss about the patients that do not come for treatment when the disease is in its early stages.

Why leprosy patients in early stages remain undetected or untreated for a long time

I. For many patients ignorance is the main cause for their remaining without treatment in early stages. This can be subdivided into three main categories:

(a) Ignorance about the very presence of the disease: This has been discussed under the heading 'need for health education'.

(b) Ignorant about the early signs: This too has been discussed like item No. (a) above.

(c) Ignorance about the curability of leprosy: Many persons do not know that leprosy is curable. That is why even when they are told that they suffer from leprosy, they take a fatalistic attitude and do not go for treatment. They do not reject the diagnosis. They accept it. But they feel nothing can be done about it any way.

II. Ignoring group: In this are patients who know that some wrong changes have been going on, in their bodies. They are not quite happy about these either. But because these changes do not cause any physical discomfort they go on ignoring those changes. They can so ignore because they do not know the seriousness of those changes.

III. Tendency to hide the disease or to reject the diagnosis: The tendency to hide the disease is understandable. This happens in crippling or killing diseases wherein people are unwilling to face the reality of diagnosis. Basically it means rejection.

Tendency to hide the disease also comes because of the fear of losing ones position in the society, howsoever lowly it may be.

Tendency to hide the disease is not seen if a disease acquires a sort of 'social status', and becomes a symbol of high status in the society, rightly or wrongly. Diabetes, hypertension, etc. can be cited as examples. However, as of today, there is no high prestige attached to leprosy. On the contrary leprosy means loss of social position.

On account of ignorance coupled with misunderstandings, etc. people react to the diagnosis in different ways, such as:—

(a) Some people may altogether reject the diagnosis on account of their false ideas regarding their family, caste, race, etc. They feel it impossible to have leprosy in their family. They take it as an affront or insult if the diagnosis of leprosy is given.

(b) Some people feel guilty when told about the disease. They feel they are sinners. They feel they are a curse on the family. They blame their own 'karma' and hide the disease, run away from the family so as not to cast their evil shadow on it.

(c) Some people are not statisfied about the diagnosis. They feel that the doctor has committed some mistake. They go on changing the doctor. They go to quacks. They go to shrines. I know of one engineer who consulted thirteen specialists, each one of whom told him he had leprosy. Why does this happen? There is a faint hope that there would be some one with a medical back-ground who would say the disease one suffers from is not leprosy.

(d) Some people hide the disease as long as is possible for them to do so. In doing this they know they are only postponing the issue. But they prefer postponing the unpleasant task of facing the disease to facing the boycott today.

All these are difficult groups to handle. They are not known to the society. They appear normal for all practical purposes. Here the problem is more than medical. It is social as well.

Aims & Objects of Health Education

We have so far seen the need for intensive health education in leprosy. We have also seen the reasons why people try to hide their disease. The significance of all these must be clearly understood by every leprosy worker. It is in this context only that we have to work and achieve some results.

What do we expect to achieve through health education? We expect certain changes in the attitudes, practices and behaviour of the society after it is exposed to Health Education. We expect these changes to be consistent and commensurate with the latest scientific information we possess about leprosy. We expect that the social sufferings of the patients will be reduced or removed, at least in the population exposed to Health Education.

Let us see in brief our aims and objects of Health Education of the society. They would be:

1. To impart basic, scientific, information—particularly that information which will help remove the superstitions, fear, wrong notions, etc. about leprosy. The main expectation here is that people will take leprosy as any other disease. So too, health education must ultimately result in changing the attitudes of the society.

2. To stress upon the early signs of leprosy and advantages of early treatment. To make people conscious about the early signs so much so that people will approach their doctors on the least suspicion.

3. To inform the people about the curability of leprosy and also about the various facilities now available for guidance and treatment of leprosy patients in their respective areas. Once people know these they need not be shunted from place to place. This will also help in yet another way. The facilities made available will be utilised to the fullest advantage by the people for whom they are meant.

Most of these aims and objects are easily appreciated and understood. Therefore, we need not go into the details of all of them. But the one concerning the change of attitudes will have to be looked into in greater depth and length. This is because leprosy workers talk loosely about change of attitudes. They feel that it is something which others have to do. They feel it to be very easy and simple. They feel that attitudes will change just by propagating certain information. It is, therefore, proposed to go into details about some aspects concerning attitudes.

Who forms our attitudes?

We receive most of our health education in our family. Our elders and our relatives, friends and peer groups impart the bulk of the information. The community in general too has its share in educating us about health, sanitation, etc.

We learn some facts of health the hard way—trial and error. But beyond doubt, this is a very costly way and we cannot afford to try this often. Some of us may learn some facts through books and journals.

There is no doubt that we receive information about health, bit by bit. The process is spread over decades, and indeed all throughout our life. Various 'Agents' of the society influence us in this respect and what we think or do about our health is a result of all such forces acting on us.

Attitudes towards health

Over the years and decades we form our attitudes towards various aspects of health. In other words we develop more or less 'fixed' or 'stabilised' ideas about a health matter. We like or dislike, love or loath, relish or resent various matters concerning health, hygiene, disease and in fact about life and death. Our family, relatives, friends

and the community all contribute in influencing our attitudes, in that order. We in turn influence the attitudes of others in the circle of our influence.

Fixation of ideas

As a result of the process of formation of the attitudes, certain 'equations' and associations are formed in public mind. These get fixed. We can search our mind to find what fixed equations and associations we have in mind about cancer, cholera, heart disease, etc. In leprosy for instance, in the minds of many, the association is that of deformity, mutilations and ulcers. Such equations may be right or wrong, scientific or otherwise. The fact remains that they are present. Effort of the health educator is to help formation of the right type of equations and associations.

Attitudes help you in stabilising yourself in the society. They relieve you of tensions and put you at ease, adjusted. They consolidate group life.

But attitudes are, after all, not altoghether that fixed nor that stabilised so as to be unchangeable. They do undergo changes. That is indeed why we see the generation gaps.

Cultural Lag—The genesis of crisis in attitudes

We live in the age of modern scientific and technological progress leading to 'explosion' of knowledge. This explosion blasts away our age-old ideas and beliefs but their replacement by new ones is neither equally fast nor equally effective. So a gap is created leading to crisis and confusion. Such a gap caused on account of the inability of the cultural set ups to change, commensurate with the technological and scientific progress, is termed the cultural lag.

One of the aims of health education in leprosy is to reduce the cultural lag. We should not only remove the wrong notions, superstitions, misunderstandings, etc., but also help formation of newer attitudes commensurate with modern scientific progress.

How attitudes influence our behaviour

Wrong notions, misunderstandings, attitudes, etc. may take long time to get 'fixed' and may remain unchanged for long. To take some examples in the field of leprosy—many people feel that leprosy is caused as a result of sin or is a hereditary disease. Many feel that it is caused by some item of food or on account of food habits and dietary patterns. All such ideas will certainly influence the thinking, behaviour and practices of the society. People may hate a patient if they believe sin as a cause of leprosy. Question of marriage in the family of a patient may acquire a different dimension if people believe leprosy to be a hereditary disease. This list can be prolonged.

Society's attitude towards disability and deformity

What is the attitude of the society towards persons having disabilities/deformities caused by reasons other than leprosy? Take the victims of poliomyelitis, burn, blindness, or the deaf mutes for instance. Does the society treat these victims as 'normal'? Is it possible for the common man to do so?

A common man will not mind the deformity if the deviations from normal is within a certain range. This range of tolerance of deviation from the normal varies from society to society.

If again, a deformity becomes a frequent occurance or if it is seen in many, then the society will not mind it. This has happened in case of pox-marks, squint, dwarfness, etc. But even these victims are not necessarily and always treated as 'normal'. Their social position and status is not exactly the same as other normal people. Social distance is bound to creep in at the time of marrige of such persons, to cite just one example.

We cannot, therefore force the society much beyond the tolerance ranges. So too, mere propagation of some facts is not going to much alter these ranges. No one can force abnormality on the normal people. If an attempt is made in this direction, it will only result in creating antagonism instead of sympathy. This is what must be happening in case of beggars or other patients with gross mutilations.

Whom to educate?

It would be ideal if each and every person living in the area of leprosy control were educated about leprosy. But is it feasible and practicable? Moreover is it really necessary to educate EACH and EVERY person? Will that help in changing the attitudes of the society?

In practice the population allotted to each

leprosy worker is so vast that he cannot physically cover all persons in his area. Moreover, health education is only one aspect of leprosy control. Workers have many other assignments on hand. How much time and energy can he give to health education?

The aforesaid factors are beyond the control of most of the workers. He does not know whom to educate. But it is necessary for a worker or his planner to be able to decide the priorities in our approach.

The rule of the thumb for deciding priorities would be to include in our effort at least all such persons who, while doing their normal day to day duties, come into contact with a large number of persons. Take for instance persons like nurses, teachers, pleaders, policemen, heads of institutions or clubs or associations, and the like. If such persons are properly educated they will, in turn, influence members of the group which they control or meet. They need not go out of their way to do so. They can do it while doing their routine jobs through their attitudes, practices and behaviour pertaining to leprosy and leprosy patients.

In this connection we cannot forget leading persons. Some leading persons are no doubt covered in the groups just mentioned. But senior officers, political leaders at various levels and other community leaders must be covered under the health education programme.

The logic behind this stress on the education of the leading persons and others mentioned is simple. Macauley's theory of 'percolation'. When we cannot cover the entire population, the information should percolate down from the higher wrungs of the society. It is reasonable to expect that with proper orientation, leading persons will slowly but surely influence the entire society.

Frequency of exposure to health education

This is one more hurdle in health education. How many times, after all, are we going to meet the same person and speak with him about leprosy? How long will the impact of our communication last? What other forces will countermand our efforts?

It must be admitted that scientific work about these aspects is not available. But it is logical to believe that people are prone to forget our teaching and that we cannot convey effectively all our points in one or few efforts. It is also reasonable to assume that the information we have communicated would need a 'brushing up' after a period of time, say two years or so.

Expectation for Cooperation

We do health education work. All the same many of our efforts go a-begging. We may be creating more confusion instead of removing misunderstandings. Why does this happen?

The health educator may not be sure of what to say to whom. Supposing for instance our listener asks a specific and pointed question after hearing us: 'What can I *do* for you'? Suppose this same question is asked by many members of the society such as a house-wife-mother, a teacher, a nurse, a gram sevak or a farmer. How would the health educator respond? How many of us have clear and specific answers to such questions? We either ask for their 'blessings' which is not going to help any one. Alternatively we expect them to do a number of things for us which again they cannot do while meeting their normal obligations to the society.

Every person has a 'role' to play in the society. When we approach him we must first fully study that role. The cooperation we expect from him should be consistent with his role. It should also be such that the person should be able to fulfill while he executes his normal duties in the normal way. We should not expect people to go out of the way to cooperate with us in our leprosy control programme.

A balance of expectations commensurate with the role of a person is the key note for the success of health education programmes. If such a balance is not struck we will not only not get the expected cooperation but may even antagonise the persons we approach for help. Take for instance a village school teacher. He has not only to teach in the school but to work for family welfare and many other programmes of the government. He is a busy person. He has now-a-days only a limited influence on the various groups of the village. If this is his role what can we expect from him by way of cooperation in leprosy control work? We can expect him to help in the school surveys whenever they are held in his school. He should get himself examined. He should also teach basic facts about leprosy to his students so that the students accept leprosy as a disease like many

others. If he suspects some student to be having early signs of leprosy, which he will do if he is conscious, he should refer the student to a proper place for guidance and treatment, and *accept* the advice given by such agencies. Above all, he should see that no student is victimised just because he or she happens to have leprosy. He can do all this in the course of his normal duties and within the premises of the school only. He does not have to spend any thing in doing this.

What information to communicate and how to communicate?

We should first study the role of a person and then decide what cooperation we expect from him. After this, it becomes easy to decide what information is to be communicated to him. Only the minimum necessary information should be communicated. We need not show off that we know such a lot. So too, we need not burden a person with information.

All said and done one must not forget to communicate to all the persons approached the following minimum information:

—Early signs, advantages of early treatment, consequences of not taking treatment in early stages.

—Curability of leprosy.

—Availability of free treatment and facilities for guidance and treatment if necessary.

Other information is added as and when needed. Information need not be communicated all in one go. We can transmit it bit by bit, but with proper clarity. However, this is possible only if we are likely to meet the people often.

But in some cases our first meeting may be our last so far as health education in leprosy is concerned. In such cases our only effort must necessarily be quite effective. We may use various audio-visual media in addition to mere talk. Pictures, flash-cards, coloured transparencies, films, posters, etc. are the various media. We can even use a combination of the media. Even here, few points should be communicated effectively rather than attempting to communicate all the information.

How is information communicated effectively? What are the difficulties in such communication? How these difficulties are overcome? These aspects will be discussed in the pages that follow.

Process of Effective Communication

The process of effective communication is explained as:

> 'In order to ensure effective communication *agent* communicates a *message* to the *receiver* through a *medium* after properly *tuning,* and watches the *feed-back* to modify the message accordingly.'

The *underlined* words in the above sentences are the key words in the process of communication. That is why some explanation of each is necessary. Communication gap or failure occurs if any one of these is not taken care of. If we know why this happens, we shall be able to avoid these and ensure effective communication.

(1) All leprosy workers are the *agents* of communication. Their interest, their conviction, their own clarity of thought, etc. will have an effect on the process of communication.

(2) The *message* or the text or content of communication is often hazy, often it is too much, or is given in a language that lay people may not understand.

(3) *The receiver's* role in the society must first be known to make our communication effective.

(4) The *medium* of communication should be consistent with the social background of the receiver. If for instance a group of Adivasis has never been exposed to films then education through movies will fail.

(5) If the receiver, the agent of communication and the medium are not properly *'tuned',* there will be failure of communication. Thus if the receiver is highly pre-occupied with some urgent pressing matter our effort of educating him about the basic facts of leprosy will fail.

(6) *Feed-back* helps us in judging whether the communication has been effective or otherwise. The reactions of the receiver will tell us about the effectiveness if we are observant. We can modify if necessary, after interpreting the feed-back. Thus communication and feed-back are going on simultaneously making communication a two way process.

Root of Conflict in Effective Communication

In choosing scientific facts to be communicated to the masses, a field worker or health educator has to rely on bits of information that occasionally trickles out of various fields of research. Often we don't get clear answers on problems relating to various aspects of the disease, its epidemiology and control, etc. and this helpless situation, while it can be effectively side-stepped in scientific sessions or conferences, becomes a great handicap for the poor field worker health-educator. What he has to impart has to be borne out of his conviction, and without vascillations; therefore it is essential that our scientific leaders are alive to the serious problem and plight of the leprosy worker and generously share with them all their knowledge and experience, and not shy way from the fact that they do not indeed have answers to a lot of problems.

The root of conflict and confusion in the minds of the health educators lies in this situation. They find it difficult to decide which information to communicate and how dogmatically and emphatically to communicate it. For convincing lay persons, certain dogma and emphasis is necessary. Only then they might give up their age old fear, and superstitions. Their attitudes, practices and behaviour will not change by evasive, non-committal and 'maybe' approach. Changing attitudes of the common man is the main objective of health education. This can happen only if the scientific information is communicated effectively. The impact of our effort depends upon the clarity, simplicity and force of the communication.

All said and done, *Effective Communication is possible.* One need not feel that effective Health Education cannot be done. We can do so provided we take care of the following:—

1. Communication of bare scientific facts is not enough

Quite often the confusion occurs because we communicate bare, scientific information. If we do this, we create a communication gap. This happens because we do not realise how the mind of a common man works. People may listen to the scientific information we communicate with admiration and even reverence. They may feel we are very superior and all that. But the information we have communicated remains for them a remote matter. They do not know how *they* are related to what we say. They fail to understand the implications of our information in day to day practice. As a result, even when they might respect us for our efforts, they do not change their own attitudes, practices and behaviours. In the communication of scientific information, therefore, it becomes imparative to link it up with day to day life situations if we want to be effective.

2. Reflecting experiences gained

Institutions devoted to leprosy work have histories of several decades of work behind them. The national leprosy control plan has been in operation for over twenty years now. However, when leprosy workers speak, they seldom reflect their experiences in their talks. Constructive, morale-building examples of actual situations are certainly experienced. But workers usually lack the urge of projecting them to the public. On the other hand sad experiences are discussed either to arouse sympathy or emotion. For changing attitudes of the society constructive experiences must be emphasised and demoralising ones supressed.

3. Communication with Conviction

When a health educator acts in contradiction of what he talks, all impact of what he says is lost. Thus we tell people that leprosy spreads as a result of close and repeated contact with an infectious patient. But if we refuse tea offered by a patient in his home, or if we do not touch patients in clinics and throw tablets at them, or hesitate to dress their ulcers, why should the patient or the society believe in what we say?

Role of voluntary agencies

The need for health education in leprosy is felt ever since organised leprosy work was started. Dr. Muir had recommended a three pronged approach viz., Propaganda, Treatment, Survey in the early twenties. Various agencies have been contributing their own mite. But before the advent of D.D.S. the stress was on in-patient work. D.D.S brought leprosy out of the four walls of the colonies. The present leprosy control plan is meant for operation right in the middle of the society. This necessitates a fresh look at the health education of the community.

The Governments have stepped in on mass scales. They have taken over the bulk of the routine work. Thousands of technicians and others have been trained and appointed

by the various governments. What then can the voluntary agencies do, particularly in the field of health education. I have the following suggestions to make:—

They can undertake—

1. Demonstrative work, setting up model units;
2. Training programmes;
3. Exploratory research;
4. Stimulating others including the governments;
5. Supplementary work—as supplementary to the Govt.

Some details of the above would be in order.

1. *Demonstrative work* such as setting of model units in various aspects of leprosy control work, including health education units can be undertaken by the voluntary agencies. The Gandhi Memorial Leprosy Foundation lead the country by starting several health education units as early as 1962. This was done well ahead of time and their experiences have come handy while planning urban leprosy work in India.

2. *Training :* This is one aspect which the voluntary agencies can make their speciality. Here again the Gandhi Memorial Leprosy Foundation started a special two months course in health education about seven years ago.

3. *Exploratory research* is something where a lot of probe, trial and error is necessary. Various experiments need to be undertaken. The Governmental set-ups have no facilities for such work. Such type of work does not fit into the pattern of grants-in-aid codes. The governments may or may not help such work. It is only the private agencies that can undertake such work and then feed the data to the governments and others to profit by it. A fine experiment is undertaken by the Poona District Leprosy Committee in the city of Poona. They are currently conducting an urban leprosy control project with financial assistance from the German Leprosy Relief Association of West Germany. Health Education is an important aspect of this project.

4. *Stimulating others to undertake work :* This is again one activity where the voluntary agencies have been seen in practice to be some what more effective than governmental agencies. Voluntary agencies can speak and criticise freely, without inhibition, without fear.

5. *Supplementary work to that of the government.* They can undertake to work according to government plans in areas demarcated for them.

In this connection agencies such as the Gandhi Memorial Leprosy Foundation, the Hind Kusht Nivaran Sangh, the Leprosy Mission, The National Leprosy Organisation can and should give a lead to other smaller agencies. They should prepare health education material for others on 'no profit, no loss basis'. Such material should be made freely available to every one desirous of doing health education work. Indeed, these suggestions apply to other aspects of leprosy control work equally well.

A central pool of persons who have worked in health education, scientists and social workers should be set up to guide others and prepare health education material suitable for various groups of the society. Such a group will reflect various points of view and enrich the material rather than make it one sided or too dogmatic.

THE PRESENT LEPROSY CONTROL PROGRAMMES IMPACT ON THE SPREAD OF THE DISEASE

DHARMENDRA

INTRODUCTION

Need for a total Concept in Leprosy Control

With reference to acute infectious diseases, 'control' of the disease is considered as synonymous with 'prevention of spread' of the disease. Thus 'control' is concerned with the 'Public Health' aspect of the disease, its 'treatment' being considered as the 'medical' aspect. In leprosy, however, the situation is quite different. In the 'prevention of spread' of this disease at present the most important method available so far is the mass scale treatment of patients with dapsone and other chemotherapeutic drugs. Thus, in this disease, the 'control' mainly depends on 'treatment, and in practice, therefore, it is '*control through treatment*'. In other words the ,medical' and the 'public health' aspects are dealt with simultaneously.

However, in a chronic and disabling disease like leprosy, associated with great social stigma, disability and deformity, the resultant socio-economic and psychological problems are very serious, and demand great attention. In this disease, therefore, the attention to only the medical and public health problems created by the disease will fail to achieve the desired end. For example, treating the patients, making them less infective and ultimately non-infective, and thus controlling the spread of the disease, without at the same time taking steps to prevent disability and deformity and their consequences, will not only discredit and hinder the control efforts, but will also produce a big back load of human suffering and socio-economic dislocation (i.e. dehabilitation) of the patients, greatly increasing the difficult task of rehabilitation.

In dealing with control of leprosy, therefore, it is necessary to direct attention to socio-economic problems, along with the medical and public health problems. In other words, it is necessary to visualise the leprosy control in its total concept, *dealing with all the three problems caused by the disease—medical, public health and socio-economic.* The socio-economic problems to be tackled with, ofcourse, have to include the important but difficult question of Rehabilitation of persons already dehabilitated, i.e. socio-economically dislocated, a discussion of which is outside the scope of the paper. *Only the control of spread of the disease is discussed here.* Ofcourse, a passing reference will be made to some of the steps necessary for achieving the objective, without going into their details.

The main features of the Leprosy Control Programme will be referred to, and especially the impact of the programmes on the control of spread of the disease will be discussed.

PRINCIPLES FOR CONTROLLING THE SPREAD OF LEPROSY

Leprosy is a preventable Disease:

Leprosy is an infectious disease, and therefore, like other infectious diseases is a preventable disease. As a matter of fact, it has been eradicated from some countries where it used to be prevalent some centuries ago, although it continues to thrive in some other countries, in many of which it creates a huge problem, and India is one of these countries.

The prevention of leprosy may be considered in the light of the measures available for the control of other infectious diseases, although several of these measures are, for the present, not available in case of this disease. The most important limitation is the non-availability of a vaccine for primary protection of the population at risk. However, as far as possible, principles applied to the control of other communicable diseases have to be applied to the control of leprosy. Of course, it is necessary to take some other measures also, because of non-availability of

means of primary protection. The principles of prevention of the infective diseases in general may, therefore, be first considered briefly.

PRINCIPLES OF PREVENTION OF INFECTIVE DISEASES IN GENERAL :

In the control of other infective diseases, there are available a number of measures which aim at dealing with the different aspects of the problem, i.e., controlling the source of infection, eliminating conditions that favour transmission, and protecting healthy persons exposed to infection.

The source of infection is dealt with mainly in two ways : (i) the patients suffering from infective diseases are kept separate from healthy people*, and their discharges are disinfected ; and (ii) these patients are treated effectively so as to cut short the period of infectivity.

The conditions that favour the spread of infection from the patient to the healthy people are dealt with by improving the sanitary and hygienic conditions including the supply of pure water, improved methods of disposal of refuse, control of vector (disease carrying insects), if any, etc.

The protection of the population at risk is achieved by increasing *specific resistance* against a particular disease by means of immunisation by vaccination or inoculation against the disease (for example cholera, small pox, enteric fever, tuberculosis, plague, yellow fever etc). The *general resistance* is increased by improving socio-economic conditions which make it possible to make available nourishing and well-balanced diet.

APPLICATION OF THE ABOVE PRINCIPLES TO LEPROSY CONTROL :

In the control of leprosy some of the above measures cannot be applied, and some others are of limited value. For example, *no method is available for increasing the specific resistance to leprosy* of healthy persons by specific immunisation. The question of *quarantine is obviously out of question* in the case of a disease with such a long and variable incubation period, and so highly prevalent in endemic countries. The *disinfection* of infective discharges, although of value, is applicable only to a limited extent. Of course it is desirable to disinfect the infective nasal discharges, and to disinfect or destroy the dressings used for the lepromatous ulcers. This precaution will, however, not be necessary in case of neuropathic (trophic) ulcers, the discharges from which do not contain leprosy bacilli.

Treatment has also its limitations, because even with the introduction of the sulphone drugs, it takes a long time to render the highly infective (lepromatous and near-lepromatous) cases non-infective. All the same, the sulphone drugs do reduce the infectivity of the patients, and are being used extensively to control the spread of the disease, by using it for mass scale treatment. As a matter of fact, this has so far been the main line of approach, and has been the mainstay of leprosy control programmes in all the countries where the disease is prevalent. *However, the development of sulphone resistance*, which is being reported to be gradually on the increase is a very disturbing and serious matter. Fortunately some other antileprosy drugs are now available, and for the treatment of highly infective (multi-bacillary lepromatous and near lepromatous cases) *combined treatment* with dapsone and some other antileprosy drug or drugs is now being advised. (This matter will be referred to later).

Because of these limitations in the use of the usual preventive methods, *some additional measures* have been resorted to in the control of leprosy. An important measure is an attempt *to find out cases in the early stage* of the disease, so that deformities and neuropathic ulcers can be prevented or minimised by early treatment ; this can be done by an intensive case-finding programme. Another important measure is the protection of children, since in endemic countries infection occurs mostly in childhood. The question of prophylactic treatment of healthy contacts with sulphones, and of building up resistance to leprosy of the contacts by means of BCG vaccination have also been investigated. Chemoprophylaxis with dapsone has been found to give over 52% protection in intrafamilial child contacts of lepromatous cases (Dharmendra et al, 1965 and 1967, and Noordeen, 1969). As far as BCG prophylaxis is concerned, the various studies have given varying results. In Uganda, where non-lepromatous leprosy predominates, among intrafamilial child contacts, the protective value of a single injection of BCG was repor-

*In case of certain diseases healthy persons known to have been exposed to infection are kept under quarantine, i.e., are isolated under suspicion till the incubation period of the disease is over.

ted to be as high as 80%. In Karimui, Papua New Guinea where the whole population received repeated BCG vaccination, the protection was 43%. In the WHO trial in Burma, the protection was found to be only 15%; moreover, three histologically confirmed multibacillary cases appeared in the vaccinated group during 1974-75. The WHO Expert Committee on Leprosy in its Fifth Report (1977) has stated "The fact that infectious forms have now appeared in the vaccinated group indicates the limited value of the measure".

CONCLUSIONS

It may be concluded that the presently available main measures in the prevention of leprosy are :—

(1) *Early detection* of all cases through case finding programmes.

(2) *Early and regular treatment* on a mass scale of all detected cases of leprosy with dapsone and other chemotherapeutic drugs in order to prevent deformities and relapses. Another objective of early and regular treatment is to reduce the infectivity of infective patients, and to finally make them non-infective.

(3) *Prevention of contact* with infective cases.

(4) *Protection of children* in contact with infective patients.

Research work is in progress which gives hope of the availability of a *protective vaccine* against leprosy, though not in the very near future. When such a vaccine is available, it will mark a great advance in the control of leprosy, because it will make possible primary protection, and thus bring leprosy control in line with control of other infective diseases in which primary protection is possible.

Further, the *raising of economic, social and sanitary standards of the population,* leading to improved diet and better housing, will no doubt contribute towards the control of the disease. However, it may be said that this step is not specifically an anti-leprosy measure. All the same it has to be emphasised that the raising of the socio-economic standard will play an important role in the control of leprosy, as also of other communicable diseases. The improved economic conditions will help leprosy control through the resulting improvement in diet and housing ; better diet builds up general body resistance against disease*, and improved living conditions restrict the chances of spread by removing overcrowding.

Necessary Means to achieve the objective

It may be pointed out that in order to achieve success in the above stated four measures, there are certain activities which will need to be attended to. These activities include : (i) *Health Education* of the population in order to make them adopt a rational attitude towards the disease and the person suffering from it ; (ii) *Education of the patient* to take proper care of his affected limbs, eyes, and nose ; (iii) *Training of persons* at all levels manning the Leprosy Control Programme ; (iv) *Adequate training in leprosy to the undergraduate medical students* ; (v) *Providing adequate number of fixed and mobile outpatient clinics* for the treatment of patients, not far from their homes ; and take all necessary steps to make the patients take regular treatment (case holding); (vi) Providing *adequate inpatient accommodation* for treatment of acute complications of leprosy or other diseases in leprosy patients ; (vii) Providing *adequate accommodation and necessary facilities for selective and short term segregation of highly infective patients,* whether early or advanced ; (viii) Total health care of leprosy patients with regard to all minor ailments ; (ix) *Welfare activities* for the patients including simple methods of domestic rehabilitation ; (x) *Protection and care of children* of leprous parents.

To put into practice the steps outlined above in highly endemic countries, a comprehensive anti-leprosy campaign is needed with a specialised leprosy service. This specialised service should be integrated with the general health services of the country in due course at an appropriate time.

The improvement in economic and hygienic conditions has to be taken up on the general plane, and is therefore not included in the above steps necessary for a specific anti-leprosy campaign.

Since the introduction of dapsone in the treatment of leprosy, the main plank in the control of leprosy has been the wide scale

* It may be stated that there is evidence to indicate that undernutrition (Vitamin, protein and caloric) depresses cell-mediated immunity (CMI) which is the main mechanism of immunity in diseases like tuberculosis, leprosy, and viral diseases.

treatment of all leprosy cases especially in the early stages and to greatest possible extent, paying especial attention to the lepromatous cases. Leprosy Control Programmes based on this principle have been adopted almost by all countries in the world including our own country. These programmes have been in progress for over 25 years in most countries including India. I would now pass on to examine what impact these programmes have made on the trend of leprosy in the countries where these have been in progress for well over two decades.

IMPACT OF THE CONTROL

The Individual Patients

The one great advantage has been that a very large number of cases have been brought under treatment, and thereby the incidence of crippling deformities has been decreased especially in the tuberculoid cases. This is no doubt a big advantage. Moreover, the foul smelling discharges from the nose and ulcers in lepromatous cases under treatment have practically been eliminated. Thus, the leprosy control programmes have been a boon to patients under treatment.

CONTROLLING THE SPREAD OF INFECTION

However, when we look for the impact of the control programmes on controlling the spread of the disease, the results have not been promising, and this has created the need of reviewing the whole matter with a view to modifying the programme by trying to remove the loopholes and bottlenecks in the programme, as also by including some additional measures which appear to be necessary.

When this programme was introduced, there was a great enthusiasm and optimism about it, and some enthusiasts believed that leprosy could be controlled in a decade or two. The little impact that has been made by the programmes has now come as a disillusionment. Except in a very few countries, and limited parts of some other countries, there has been no change in the trend of leprosy.

EVIDENCE ON WHICH THE ABOVE VIEW IS BASED

The World Health Organization has been evincing great interest in expanding these programmes, and in collaboration with UNICEF has been instrumental in bringing into existence and rendering help to them in various ways. In the Fifth meeting of the World Health Organization Expert Committee (1977) one of the items (1.6) relates to "The effect of control measures". The first paragraph of this item is reproduced below.

> "Despite the undoubted value of the treatment programmes to individual sufferers from leprosy, the limitations of the control measures in ensuring that others will not become infected are evident from the continued appearance of new cases. Doubts about the efficacy of the treatment measure have been intensified by the recent findings that sulfone therapy cannot by itself ensure the total eradication of all viable bacilli in the patient with lepromatous leprosy. Moreover, secondary prevention must remain an imperfect tool in the control of leprosy transmission as long as it is not possible to identify infectious cases immediately they become a danger to others. In addition, serious operational problems are often encountered in carrying out control measures."

After making this general statement, the Report goes on to say in the second paragraph : "Nevertheless, there is substantial evidence that a significant decline of the disease in the community, shown not only by lowered prevalence rates but by reduction in incidence, is effected by present control measures, of which the main element is sulfone chemotherapy." In substantiating this statement, a reference has been made to the findings in Thailand and Burma.

LEPROSY CONTROL IN THAILAND AND BURMA

In both these countries control projects have been in progress for more than 15 years. "Random sampling surveys conducted at 10 year intervals have shown significant reductions in the prevalence rates. In Khon Kaen Province, Thailand, the prevalence fell 70% from its initial (1962) level of 12.37 per thousand, and in central Burma there was a similar reduction from an initial (1963) level of 32.0 per thousand. Results from certain francophone African countries are comparable."

"The data from the second surveys have confirmed the accuracy of the greatly lowered incidences suggested over successive years by case detection figures. The latter are derived from school surveys, contact surveillance, and voluntary reporting by new patients. While these modes of detection have become more efficient over the years, the number of new

cases recorded annually has fallen. An important factor in the epidemiological trends was the finding in both surveys that more than 75% of the estimated bacilliferous cases were under treatment (Khon Kaen, 76% ; Central Burma, 90%). A considerable number of early tuberculoid cases have been found in such surveys, but many are likely to have been self-healing."

In relation to the assessment of the results, the importance of incidence rates has been duly recognised. It is stated : "The incidence rate is an accurate index of continuing transmission, but it is particularly difficult to ascertain retrospectively because of the imperfect histories given by patients and the tardy reporting of signs and symptoms. Serial surveys would have to be conducted annually to reveal most of the new cases, and this is clearly impracticable. However, annual surveys of a limited number of randomly chosen villages over a period of 5-10 years would allow reasonably accurate incidence estimates to be made."

As to the importance of prevalence rate, it is stated "Knowledge of prevalence rates is essential in order to assess the size of the leprosy problem". However, because of various factors influencing the prevalence rates, these rates are not considered suitable for accurate assessment.

The report also mentioned comparable results from certain francophone African countries.

Finding in Tropical African Countries

In this connection, a reference may be made to the article of Martinez Dominguez and Bechelli (1977) giving an assessment of impact of control measures in Tropical African countries. They have referred to the leprosy campaign in 26 countries of tropical Africa. The Leprosy campaign in tropical Africa started, in a big scale, in the fifties especially in French speaking countries, after a relatively effective antileprosy treatment was made available and leprosy control could be taken into consideration by Public Health Authorities. According to Bechelli and Martinez (1966) in a majority of these countries leprosy prevalence was above 10 per thousand, reaching 40 per thousand and more in some of them.

In the paper under reference, an attempt has been made to assess (i) the evolution of leprosy endemic in these countries, (ii) the impact of the control measures upto now, and (iii) the prospects of controlling the disease taking into account the present means and resources and socio-economic changes in process after independence.

In the present context we are, of course, specially concerned with the impact of control measures on the control of the disease. The authors have however remarked that the reliability of these data for most of the countries has to be treated with reservation. Their findings are summarised below.

(i) *Prevalence of the disease.* Out of the 26 countries, the registered number of cases of leprosy showed an increase in 18 countries, and a decrease in 8 countries.

The authors have remarked that the epidemiological significance of these variations in the registered cases is not clear as these changes could be due to various factors, and may not necessarily indicate actual increase or decrease in the number of cases. For example, an increase in the number of registered cases may not indicate the actual increase in the number of cases, but may be due to (a) better case-finding and case-holding ; (b) non-removal of inactive cases from the list of active cases, thus artificially inflating the number of active cases ; and (c) increase in population. (The present author would like to draw special attention to the role of these factors in case of the rising estimated number of cases in India). On the other hand, reduction in the registered number of cases may indicate a real decrease in the prevalence rate as a result of correct application of control measures ; but the decrease in the number of registered cases in most instances is likely to be due to operational inefficiency (poor case finding, high proportion of cases having discontinued treatment for one reason or another, and therefore having been removed from the list of registered cases).

(ii) *The number of newly detected cases.* Only the incidence rate of the disease in successive years gives correct information about the trend of the disease in an area. However, when case finding is correctly done, the case detection rate throughout a long period and the proportion of lepromatous cases in the newly detected cases may give some idea of the incidence of the disease in this area.

Data about these rates is given for three of the African countries. The detection rate remained stable in one country, and showed a

decrease in the other two countries. However, in the country "where the greatest reduction of registered number was observed (67%), this was not paralled by the reduction in newly detected cases. Moreover, it was noted that the percentage of the newly de'eced lepromatous cases among the newly detected cases is not decreasing. This is a good indication to suggest that the ceiling of case finding has not yet been reached in these countries, and there must be many untreated old cases." From these data it is concluded "it seems that the incidence has not yet been significantly or really modified uptodate". In support of these views regarding many cases still remaining undetected they quote the findings of the WHO Leprosy Advisory Team (LAT) in Africa (Northern Nigeria, North, Central and South Cameroun). "In random sample surveys showed that even in countries with a fairly good case-finding, new cases amounting to 75% of the number of registered cases were detected (Bechelli and Martinez, 1966). They also quote Laviron (1970) who feels that on the whole only 40% of the total estimated number of cases existing in AFRO* have yet been registered, and of the registered cases only 50% are under treatment.

As a general appraisal, and according to available data, they have reached the following conclusions :

(i) The number of registered cases has increased in the majority of countries, but the significance of this feature is not clear, as in many countries inactive cases are kept indefinitely on the registers**, and there is no increase in population ;

(ii) Uptodate there is no conclusive evidence of any change in the incidence ;

(iii) It is not possible to perceive any epidemiological change affecting the trend of leprosy endemics in the countries under study ; and

(iv) Irregularity of treatment, and bacteriological positivity of lepromatous cases under treatment with sulphones* favour the maintenance of leprosy endemicity.

Regarding the future prospects of control of leprosy in tropical Africa, the authors state that due to adverse socio-economic, hygienic and sanitary conditions, the limitations of antileprosy drugs, irregularity of treatment, lack of a vaccine etc., the control of leprosy in many countries may be delayed for numerous decades, if not for centuries, if control measures are not well applied, and if socio-economic and other conditions are not improved.**

FINDINGS IN INDIA

The Hugeness of the Problem

India has a very huge leprosy problem. The exact number of cases is not known, which is also true for many other countries. The estimated number of cases in the whole world now stands betwen 12-15 million and India is supposed to be responsible for about 1/4th or 1/5th of the total world leprosy.

Estimates about the number of leprosy cases in India have been made from time to time on the basis of projection of the known number of cases at different times. With progressive increase in the attention given to the disease, especially to the increased attempts at case-finding, the number of known cases of the disease has been on the increase, and this increase has naturally been reflected in the estimated number of cases of this disease. The knowledge about the extent and distribution of the disease in India was very meagre before the Indian Council of the British Empire Leprosy Relief Association (predecessor of the present Hind Kusht Nivaran Sangh) carried out leprosy surveys in different parts of the country during nineteen twenties and thirties. As a result of these surveys carried out in various parts of India, and by multiplying the detected number of cases by a certain factor, it was estimated that the number of cases in the country would be about 10 lakhs, i.e. 1 million. Since then antileprosy work in the country has been

* AFRO, the who Regional Office in Africa deals with 40 countries.

** This was one of the reasons given by Dharmendra (1976) for the progressive increase of estimated number of cases in India; the other reason being the explosive rise in population of the country. In case of regional increase in some big cities, and industrial centres the reason for the increase was migration to such places in search of employment, and this did not affect the overall prevalence in the country.

* The infectivity of 'Open' cases of leprosy under treatment with sulphones was stressed by Dharmendra (1974)

** The remarks may perhaps be true for many countries outside Africa.

intensified especially in the post-independence years after 1948, and particularly after the initiation of the National Leprosy Control Programme in 1955 ; the estimated number of cases has been rising from 10 lakhs to 15 lakhs, 25 lakhs, and the figure now stands at 32 lakhs. The figure of 25 lakhs (25,00,000) was based on the total population of the country in the 1961 census. With considerable increase in the population, as reflected in the 1971 census, the estimated number of leprosy cases has been revised upwards to 32 lakhs.

NO EVIDENCE OF INCREASE. The progressive increase in the estimated number of cases in India has sometimes been interpreted to imply that leprosy is on the increase in the country. This interpretation is, however, not valid. There has no doubt been an increase in certain big cities and industrial areas, but that has been due to fairly large scale migration from the rural to the urban and industrial areas. However, there is no evidence to show that there has been an actual increase in the prevalence rate of the disease in the country as a whole. This view is supported by the fact that in a few areas where long term systematic investigations have been carried out, there has been no evidence of any increase in the prevalence of the disease.

Apart from the increase in population, the main reason for the increase in the estimated number of cases is the increased activity in the case-finding programme. A contributory factor in this respect is that, because of the availability of potent drugs for the treatment of the disease, an increasing number of cases are voluntarily seeking treatment. Both these factors have resulted in an increase in the estimated number of cases. Still another factor for the progressive increase in the number of estimated cases in India is the fact that till recently no attempt was made to remove from records the 'disease-arrested' or 'cured' patients. Only recently attention has been drawn to it, but the results reported in this direction are still too meagre to have any bearing on the total estimated cases in the country as a whole.*

One definite result of the expanding National Leprosy Control Programme has been that it has made us aware, more than ever before, of the hugeness of the problem. Moreover, it has been instrumental in making available modern treatment of leprosy to about 1.6 million (16 lakhs) patients i.e. 50% of the estimated cases. However, it is not correctly known as to how many of the registered cases are actually taking treatment regularly.

With further intensification of the case-finding programme, the number of known cases will no doubt increase, and with that, the estimated number of cases. This is bound to continue till all or nearly all cases of leprosy in the country are registered, when the actual number and the estimated number will approximate.

It is possible that this figure (32 lakhs) may be close to the actual figures ; with further intensification of the case-finding programme leading to an increase in the number of known cases, and with further rise in population at the next decennial census, the estimated figure will of course markedly rise further.

IMPACT OF THE NATIONAL LEPROSY CONTROL PROGRAMME ON SPREAD OF THE DISEASE. Although the National Leprosy Control Programme of India has been in existence for the last over 20 years, and has been greatly expanded during the years, it cannot be said with any degree of certainty as to what extent it has succeeded in controlling the spread of the disease. A large number of patients have individually benefitted, and the deformity index has gone down wherever this programme has been carried out fairly satisfactorily. However, very meagre data is available to assess the effect on transmission of the disease, the accurate information about which is given by a sustained decrease in the *annual incidence rates* of the disease which is different from the case detection rates per year. The case detection rate simply means the detection of previously undetected cases per year or for a number of years. Whereas *the incidence rate is* calculated by the number of *newly detected cases amongst persons who had been seen earlier and recorded as free from the disease*, per year ; and if the figures have been pooled for a number of years, then number of 'new cases' in the above sense are divided by the number of years they cover. Case detection rate is not synonymous with incidence rate, as detection rates are subject to several factors such as missing of cases amongst population previously examined,

* However, it is important that no targets be fixed for this purpose as in doing so there is a danger of the figures being inflated in the other direction, due to desire of the workers to meet the targets, or even going beyond them.

newcomers in the area, etc. Prevalence rates also suffer from similar disadvantages.

The Indian Council of Medical Research is engaged in a project for assessing the results of the Leprosy Control Programme, but its findings are not yet available. However, a study taking into account the detection rates reported by Kapoor (1976) in certain areas in Maharashtra may be intrepreted to indicate that the Leprosy Control Programme measures in these limited areas have been fairly satisfactory. Some particulars about the 3 sectors included in the study are given below :

The number of cases detected in each quinquennium (in case of Barsi, the 1st quinquennium actually consists only a 3 year period) is reported in 6 tables, 2 for each sector—one for children and the other for adults. The reduction in 'case detection' has been indicated as a percentage in 'incidence' whereas actually it represents only a reduction in case detection rate (the distinction in 'incidence' and 'case detection' has already been pointed out earlier). The number of lepromatous cases, and the lepromatous rates in the newly detected cases is also indicated. In addition to the reduction in case detection, there has been a marked reduction in deformities, and consequently in percentage of deformity in the newly detected cases. The reduction in the number of newly detected cases, as also the percentage of reduction, and the information about the L rate is summarised here in the following two tables—one for children and the other for adults.

Discussing the findings, Kapoor makes the following statements.

In Children. In Vairag the incidence** has been decreasing in every quinquennium, and that the reduction between the last two quinquennia is 20%. This strongly suggests that leprosy in children is definitely reduced. In the Barsi and Gondia sectors also (taking 1966-70 figures as a base) the detection in incidence (actually detection rate) shows a reduction of 45.7% and 43.9% respectively when the 1966-70 figures are compared with 1971-75 figures ; however, before expressing a definite opinion, he would like to wait for the findings in the coming years.

He further points out that lepromatous and deformity rates have been considerably decreased.

In adults. Having decided to take the period 1966-1970 (the third quinquennium) as the base, there was practically no difference in the detection rates in the Vairag Sector between the 3rd and 4th quinquennia (being 1.76 and 1.75 per thousand per year respectively). However, between the second and third quinquennia it was 13.3% (case detection rates being 2.03 and 1.76 respectively).

The reduction in the Barsi and Gondia Sectors between the 2nd and 3rd quinquinnia was 26.29% and 33.09% respectively. Kapoor stated that it was necessary to watch the situation for another 5 years before coming to a definite conclusion.

Sector	Population under study	Prevalence rate per 1000	Control work started	Quinquennia for which results reported			
				1st	2nd	3rd	4th
Vairag	17500 (1951 census)	Over 20	1955*	1956 to 1960	1961 to 1965	1966 to 1970	1971 to 1977
Barsi	15200 (1961 census)	Over 20	End of 1963	1963 to 1965	1966 to 1970	1971 to 1975	...
Gondia	28000 (1961 census)	8	Towards the end or 1959	1961 to 1965	1966 to 1970	1971 to 1975	...

* One of the first centres opened under the scheme, and also one of the best centres.

** Actually detection rate

CHILDREN

(0 - 14 years)

Period	VAIRAG				BARSI				GONDIA			
	New Cases		L Cases		New Cases		L Cases		New Cases		L Cases	
	No.	Detection rate*	No.	L rate	No.	Detection rate	No.	L rate	No.	Detection rate*	No.	L rate
1956 to 1960	67	2.33	7	10	...	...	...	...	...	...	...	...
1961 to 1965 (In Barsi 1963-65)	36	1.10	4	11	35	1.95	1	3	13	0.17	1	3
1966 to 1970	65	1.90	0	0	107	3.29	3	3	36	0.43	1	3
1971 to 1975	57	1.52	2	3	60	1.78	0	0	22	0.24	0	0

* Detection rate per thousand per year

Reduction in detection rate between the last two quinquennia	20%	45.72%	43.93%

ADULTS

(15 Years and above)

Period	VAIRAG				BARSI				GONDIA			
	New Cases		L Cases		New Cases		L Cases		New Cases		L Cases	
	Total No.	Detection rate*	No.	L rate	Total No.	Detection rate*	No.	L rate	Total No.	Detection rate*	No.	L rate
1956 to 1960	202	4.40	43	21	...	...	...	...	...	...	...	...
1961 to 1965 (In Barsi 1963 to 1965)	99	2.03	26	26	164	6.0	74	45	162	1.42	42	26
1966 to 1970	94	1.76	16	17	172	3.53	52	30	176	1.40	27	16
1971 to 1975	98	1.75	14	14	139	2.60	20	14	129	0.93	24	19

* Detection Rate per thousand per year

Reduction in Detection Rate between the two quinquennia	Between 2nd and 3rd quinquennia 13.3%	Between the last 2 quinquennia 26.9%	Between the last 2 quinquennia 33.09%

There has been a decrease in deformity and lepromatous rates in Vairag and Barsi Sectors. However, in the Gondia Sector, there has been a slight increase.

Prevalence rate. In the present study change in the prevalence rate has not been worked out. However, under the ICMR Assessment Project, according to Dr. Kapoor, Dr. Wardekar found a definite reduction in the groups of villages selected for study both in the Vairag and the Barsi Sectors. Thus, Kapoor's findings strongly suggest reduction of leprosy as a result of the Leprosy Control Programme in the villages studied.

Kapoor remarks that possibly the case detection rate (incidence rate as used by him) of leprosy substantially declines in the first 10-15 years after the introduction of the control measures, but the reduction then slows down.

Conclusion;

It can therefore be concluded that in a few countries, and in a few centres in India, the dapsone based leprosy control programme had had an impact on the spread of the disease. The general impression is that in most countries, and in India as a whole, there has not been much impact of the programme on controlling the spread of the disease. In India several people have been expressing the view that leprosy is on the increase. While the writer agrees that in general there has been practically no impact on controlling the spread of the disease in our country, he does not agree that the disease has been on the increase. However, there could be an increase in future because of the progressively increasing development of dapsone-resistant patients, if proper and adequate measures are not taken to prevent such a situation developing.

Having discussed the impact (or general lack of impact) of the control measures adopted so far, it is proposed to discuss some of the factors considered responsible for the situation, as also propose some possible measures to remedy the defects.

THE FACTORS RESPONSIBLE FOR FAILURE

The National Leprosy Control Programme in our country has been progressively expanded, and it is now proposed to further expand it quickly in order to 'cover' all the endemic areas of the country within the present plan period. It is quite an encouraging proposal as far as it goes. However, if we accept that in general the Programme has failed to achieve the desired end, we should try to find out the factors responsible for the failure, and the possible ways in which the defects can be remedied. I shall not refer here to the great need of improving the socio-economic and hygienic condition of the population in general, because that does not form an integral part of of the National Leprosy Control Programme. I shall also not go into the need for gearing up the Administrative Machinery because this matter is under constant review, and necessary steps are being taken in this direction as far as possible. I shall try to pinpoint some other basic and important factors which need special consideration. These factors can be grouped as under :

(1) The specific chemotherapy—Limitations of.

(2) Infectivity of multi-bacillary patients under treatment.

(3) Need for ensuring regular attendance of the patients registered for treatment.

(4) Strengthening Health Education concerning the disease.

(5) Need for adequate training in leprosy to the entire medical profession.

(6) Need for protection of children, including family planning on a voluntary basis.

(7) Role of Leprosy Hospitals.

I shall now touch briefly upon the points listed above.

(1) *Specific Chemotherapy*

The Sulphone Drugs. The introduction of the Sulphone drugs in 1940s revolutionised the treatment of leprosy. It brought new hope not only for the patients, but also for controlling the spread of the disease through mass scale treatment of the patients. At the start only derivatives of the mother sulphone diaminodiphenylsulphone (DDS) were used, but later DDS itself was found safe in small doses. (DDS is commercially known as dapsone). Dapsone became and has remained the first line of treatment of leprosy, although it is slow in action, and takes a very long time to make an infective patient non-infectious. It has been found to be an effective and inexpensive drug, safe in the doses used, and is easy of administration. This was

therefore adopted as a basis for the mass scale treatment of the disease in campaigns for the control of leprosy. This method of leprosy control has been adopted by all countries with a leprosy problem throughout the world. India which is responsible for about 1/4th to 1/5th of the total world leprosy also adopted this method of Leprosy Control, and has in operation a big National Leprosy Control Programme primarily based on mass scale dapsone therapy, ofcourse, with other necessary accompaniments.

Limitations of dapsone. Faith in dapsone as the mainstay in the treatment of patients and in the control of leprosy was no doubt justified. However, in the recent past there has arisen a situation which clearly indicates that although Dapsone still remains the mainstay in the treatment of leprosy, treatment with this drug alone cannot be depended upon for controlling the spread of the disease. This is because of (i) development of sulphone resistance and (ii) persistance of sulphone sensitive bacilli even after long periods of sulphone therapy. The mechanisms of these two phenomena are of different nature, and as a matter of fact the mechanism of persistance of drug sensitive bacilli is not well understood. The two matters will therefore be briefly considered separately.

(i) *Dapsone Resistance.* In a percentage of patients under treatment with this drug, there occurs a stage when the leprosy bacilli in their bodies are no longer sensitive to dapsone, rendering the drug inactive in such cases ; in other words, dapsone-resistance develops. As a result, these patients who had previously been progressing under treatment, no longer respond to it, and their condition begins to deteriorate even under continued treatment with the drug. It may be stated that development of Sulphone Resistance has been reported only in multi-bacillary (lepromatous and near lepromatous) cases.

The development of sulphone resistance affects not only the patient concerned, but also the community at large, because such patients will spread leprosy with the dapsone resistant strains of the bacilli, and the persons thus infected will not respond to treatment with dapsone even at the start of treatment i.e. there will be primary or pre-treatment resistance. There is also some evidence to the fact that this process has already started as would appear by a recent publication of Pearson et al (1977). So far it was believed that primary i.e., pre-treatment dapsone resistance was not seen, or if present, it was very rare. Pearson et al have reported on 8 patients from Ethiopia, 5 with primary dapsone-resistance confirmed by the mouse foot-pad method. This clearly demonstrates that "Persons living in areas where acquired dapsone resistance is common may be infected with dapsone-resistant strains of *Mycobacterium leprae*."

The problem of dapsone-resistance of *Myco. leprae* is no doubt a serious one, but fortunately means are available to face the problem. *There are a number of other anti-leprosy drugs available, the use of some of which in combination with dapsone is very likely to prevent the development of dapsone-resistant strains of the leprosy bacillus.* The most potent of all these drugs is Rifampicin, and combined treatment with these two drugs (dapsone and rifampicin) appears to be the obvious method for preventing development of sulphone resistance. The most economic two-drug regimen, a combination of sulphones with rifampicin, is that suggested by Pattyn et al (1974 and 1975) i.e., the two to three months introductory treatment with rifampicin 600 mg daily or 900 mg weekly, followed by daily dapsone. Another combination recommended is that of dapsone and clofazimine. However, Pattyn et al (1975) found clofazimine slow in action and of no value except as an additive to the introductory treatment with intermittent Rifampicin.

Need for multi-drug treatment. Drug resistant strains of *Myco. leprae* are known to develop sooner or later with all the presently available anti-leprosy drugs (including rifampicin). As a matter of fact, dapsone is the best drug from this point of view as secondary resistance to it develops after a very long time, the earliest recorded case has been after five years of treatment, and the period before secondary sulphone resistance develops may even be 20 years or longer. Because of the danger of resistance developing against all the drugs so far used alone i.e., as monotherapy against leprosy, it is being generally recognised that in the combined therapy of mycobacterial diseases, instead of the treatment being a two-drug therapy, it should be a combination of 3 to 4 potent anti-mycobacterial drugs. Thus, at the Forschungsinstitut, Borstel, Germany, as reported by Freerksen (1975b), a four-drug regimen of multi-drug therapy has been evolved for the treatment of

all mycobacterial diseases including tuberculosis and leprosy. This four-drug regimen includes Rifampicin, Dapsone, Prothionaamide and Isoniazid (INH) ; the last three drugs are included in a single tablet known as Isoprodian. This treatment is therefore designated as Rifampicin plus Isoprodian. Several short term trials of this four-drug therapy in leprosy have been carried out; and satisfactory results were reported at the Second International Leprosy Colloquium held at Borstel in Germany, and have been published in the Supplement to Leprosy Review, Vol. 46, 1975. However, the satisfactory results could refer only to the clinical and bacteriological improvement in the patients treated with it for short terms, and it is too early to say how much effect they will have on delaying or eliminating the development of Dapsone resistance, and prevention of relapses while treatment with this drug is continued. For a conclusion to be reached in this matter, long term studies are needed, and are in progress. Treatment with one single drug (mono-therapy) including treatment with dapsone or rifampicin sooner or later gives rise to drug resistance. Therefore, multi-drug therapy in leprosy for multibacillary cases—lepromatous and near lepromatous cases—has become as essential as in any other mycobacterial disease in which it has become a common practice to use multidrug therapy.

Need for inexpensive multi-drug therapy. However, at present, and till it is freely available at a considerably lower price, it will not be possible to use on a large scale a multidrug therapy regimen in which rifamipicin is one of the constituents, because of the impracticability of its use in developing countries where 95% of the present day leprosy problem exists. Therefore, till the price of rifampicin comes down greatly and/or till inexpensive but effective intermittent regimens for use of rifampicin are evolved, it is essential to develop economic methods of multi-drug therapy in leprosy by combining dapsone with some other anti-leprosy drugs which may not be as potent and as effective as the four-drug formula of dapsone, rifampicin, isoniazid and ethionamide (or prothionamide). For the purpose of evolving an inexpensive multi-drug therapy for leprosy, attention is invited to the two drugs—Isoniazid and Thiacetazone—for combination with dapsone. The value of isoniazid and thiacetazone in the treatment of Tuberculosis was first demonstrated in East Africa, and was later confirmed by the Tuberculosis Investigation Centre, Madras (1963 a & b), established by the Indian Council of Medical Research for evolving inexpensive regimens for the treatment of pulmonary tuberculosis. The results of the Madras Centre were confirmed by several other workers in India. It may be said that these two drugs in one tablet (under different trade names and various strengths) are widely used in India as a follow-up treatment of pulmonary tuberculosis.

There is some reluctance, especially by dermatologists, to use these two drugs in combination with dapsone. This is due to the fact that isoniazid in high doses causes peripheral neuropathy in a percentage of patients ; and that thiacetazone causes allergic dermatitis in a small percentage of patients. As regards isoniazid, the experience of the Tuberculosis Chemotherapy Centre, Madras (1963) is that small doses of isoniazid upto 300 mg per day do not cause any peripheral neuropathy, and that bigger doses (400 and 650 mg daily) produce neuropathy in a percentage of cases, but that it can be prevented by giving a small (6 mg) daily dose of pyridoxine ; however, there is no advantage in using these higher doses. As to the importance of isoniazid in a regimen of a combined therapy for mycobacterial diseases, it may be said that at the Forschungs-institut, Borstel, Prof. Freerksen (1975 a) found that all the three-drug combinations investigated by them were found to be effective only if isoniazid or ethionamide was one of the constituents. As regards the allergic dermatitis produced by thiacetazone, the Tuberculosis Chemotherapy Centre, Madras (1966) in a controlled study with isoniazid-thiacetazone and isoniazid-PAS, found that cutaneous hypersensitiveness developed in 5 of the 75 patients of isoniazid and thiacetazone combination, 3 occurred in first month and 2 in the second month. Similar cutaneous hypersensitiveness was found in 4 of the 71 cases treated with the combination of isoniazid and PAS, though the condition was usually more severe in the thiacetazone group. On account of this allergic dermatitis appearing in a small percentage of cases, there is of course need for being vigilant in the first three months during combined treatment with isoniazid and thiacetazone, since toxic effects, if any, are manifest during the first 12 weeks. However, there is no justification of rejecting the combination altogether. Caution in the matter is no doubt necessary, and for this purpose it is proposed that for the first three months the combined tablet should contain

only 25 mg of thiacetazone. As combined tablets containing different strengths of the two drugs are readily available in India, there should be no difficulty in this respect. Any patient sensitive to thiacetazone can thus be detected and excluded from this combined treatment and put on dapsone, isoniazid and another anti-leprosy drug like thiambutosine which does not produce drug dermatitis, and which was at one time considered to be the 2nd line of treatment of leprosy, dapsone being the first thiambutosine has also been used in combination with Rifampicin by Rees and his group (Rees, 1975).

Not a new idea. The use of the combination of DDS with isoniazid and thiacetazone in the treatment of leprosy patients is not altogether a new idea. The combination has been used as a follow-up treatment of patients suffering from both leprosy and tuberculosis since a long time at the Central Leprosy Teaching and Research Institute at Chingleput in South India ; it was in vogue when the present author joined as Director of the Institute in 1957, it was continued during his tenure till 1966, and it is still in use as ascertained from the present Director. The treatment consists of giving dapsone in prescribed doses for the treatment of leprosy, together with treatment of tuberculosis on the followingl ines—streptomycin 1 gm given intramuscularly with 300 mg INH daily till 50 to 60 gm of streptomycin has been given, and then treatment is continued with 300 mg. INH and 150 mg. thiacetazone (adult dose) for as long as it is found necessary. Thus, at this Institute, treatment of patients suffering from both leprosy and tuberculosis consists at first of a combination of dapsone, streptomycin and INH, and later streptomycin is replaced by thiacetazone. Under this combined treatment there is improvement in both the leprous and tuberculous conditions. Since no control trial has been made, it is difficult to say whether improvement in the leprous condition was more marked in patients under combined treatment than in the leprosy patients treated with dapsone alone. However, in the experience of the present writer, as also of the present Director, there have not been observed so far any complication of peripheral neuropathy due to continued use of INH, or any complication of exfoliative dermatitis due to the continued use of thiacetazone in the doses prescribed.

Further, during the discussion on combined treatment at the Borstel Colloquium, Molesworth (1975) gave the information that in Malawi thiacetazone and isoniazid were being given to leprosy patients on treatment with DADDS ; and he strongly advocated the use of a combined tablet of isoniazid and thiacetazone. At the request of the present writer, Molesworth (1977) supplied further information on the subject which is abstracted here, as it has a direct bearing on the subject under discussion. The points that emerge from his letter are : (1) he entirely agrees with the present author's view regarding the combined therapy with dapsone, thiacetazone and isoniazid for treatment of multi-bacillary leprosy patients, and also with the dose of the three drugs suggested for the adult patients ; (2) he has given up DADDS because it releases very small doses of DDS, even smaller than the sulphetrone injcctions used by him earlier in Malaysia, when it was used as a monotherapy, and that he wae now using 50 mg dapsone per day instead ; (3) to regulate the combined treatment in adults and children they have got combined thiacetazone-isoniazid tablets in two strengths, HT_3 tablets for adults (containing 150 mg thiacetazone and 300 isoniazid) given once a day, and HT_1 tablets for children (containing 50 mg thiacetazone and 100 mg isoniazid); of the children's tablet 1 or 2 are given per day according to the weight of the child till he is big enough to get the full dose i.e. one HT_3 tablet a day ; (4) he does not get cases of peripheral neuropathy with the doses used, and does not expect any, except by accident ; (5) he has met with only 3 cases of dermatitis due to the thiacetazone content out of several thousands treated, and all the three responded rapidly to withdrawal of treatment ; of the three cases, two had only miliary itching erythema, the third was more severe with exfoliation and needed corticoids ; (6) the very few cases which are found sensitive to thiacetazone can be treated with alternative drugs (as also suggested by the writer of this note); (7) in his experience the results with dapsone-thiacetazone and isoniazid have been the same as those reported with rifampicin plus isoprodian i.e. a very rapid fall of MI to zero, and the BI diminishing very slowly.

In the absence of experience it is not claimed that the suggested inexpensive combination (Dapsone 50 mg, thiacetazone 150 mg, and isoniazid 300 mg) will be as efficient in preventing development of dapsone resistant strains of the leprosy bacillus as the combination or combinations containing rifampicin which is an extremely expensive drug and is not freely

available. However, the suggested combination is expected to be of definite value in this respect. The problem of preventing development of dapsone-resistance is so urgent that one should not wait till the cost of rifampicin is considerably reduced, and/or till a considerably less expensive regimen of intermittent administration of the drug has been established. The urgency of the matter demands that till either of the two objectives is achieved, something must be done for the treatment of multi-bacillary leprosy patients in an attempt to prevent the progressive increase of sulphone-resistance, both primary and secondary, in developing countries, in which the main leprosy problem of today exists. For this purpose the above suggested inexpensive formula appears to be the most feasible solution.

The use of clofazimine for the combination is not being purposely suggested for two reasons : (i) like rifampicin, it is also an expensive drug, though not as expensive as rifampicin ; (ii) the pigmentation it produces is not liked by a large number of patients for aesthetic and social consequences, especially on account of pigmentation in the face. The use of clofazimine should be reserved for purposes where it is especially indicated, viz. acute reactions in borderline and tuberculoid cases, recurrent chronic reactions especially in the steroid dependent patients, in acute neuritis, etc.

Bacterial Persistence. Another cause of relapse in lepromatous cases is due, not to the development of drug-resistanct strains of *Myco. leprae*, but due to persistence of drug-sensitive organisms when dapsone or any other antileprosy drug is discontinued after a long period of its administration, and practical arrest of the disease. With dapsone it has been reported even after 10 years of continuous treatment. It has been reported in cases on rifampicin and clofazimine as also under multi-drug therapy. Unless relapse occurs, the presence of very small numbers of viable and drug-sensitive bacilli are found especially in nerve, muscles, smooth (dartos) muscle and other places. The mechanism of this persistence is not clearly understood. It used to be considered to be due to the organisms lying protected in nerves and other tissues where dapsone could not penetrate, and it was expected that rifampicin by penetration into these tissues would solve the problem of 'persistence' of viable drug sensitive bacilli. However, this hope has not materialised as Rees (quoted by Gelber, 1976) found persistent bacilli even after 5 years of rifampicin treatment. Moreover, Allen et al (1975) have shown that dapsone, rifampicin, isoniazid and pyrazinamide can all penetrate the nerves of sheep and dog.

Because of the 'persistence' of the bacilli, which in some cases can multiply after the cessation of treatment and thus cause a relapse of the disease, several workers advocate life-long treatment of lepromatous leprosy. However, the view of Prof. Freerksen (expressed during the discussion on drug resistance) appears to be more rational and practicable. Freerksen (1975 c) states "At the present level of our experience we must have the courage to terminate a treatment after a sufficiently long observation period during which the patient remains negative*, and then investigate thoroughly the occurrence of relapse". He further adds "This of course must be done in hospitals chosen for the purpose, and with the help of suitable doctors. Of course if the relapse occurs, another course of treatment has to be given."

(2) *Infectivity of Multi-Bacillary Cases under Treatment.* As already stated, Bechelli and Martinez (loc. cit.) while writing about the impact of anti-leprosy measures in tropical Africa consider that one of the reasons for the continuous spread is the infectivity of patients under treatment. This has obviously a reference to a patient being considered as non-infective when all the bacilli found in smears from skin or nose are non-solidly stained i.e. when the MI is negative. This point was also emphasised by Dharmendra (1974). Concluding his article he had stated : "It can therefore be concluded that the question of all non-solid forms of the leprosy bacilli being degenerate and non-viable is still a very highly controversial matter."....,,In the author's opinion it would be wise to stick to old criteria based on bacteriological negativity (BI zero) of multiple skin smears, and maintained at examinations repeated over 3 consecutive months." Dharmendra (1977) again referred to this matter in detail, and made the following observations regarding the significance of variations in morphology and staining characters.

The typical morphology : Typically, the leprosy bacillus is a straight or slightly curved slender rod varying from 6 to 8 micron in length and 0.5 to 1.0 micron in breadth. They are acid-fast, i.e. when stained with a

* As judged by negative BI and not by negative MI

strong dye (carbol-fuchsin), they are not decolourised by dilute acids ; when stained with the Ziehl-Neelsen stain, the bacillus is stained bright red uniformly throughout its length.

Variations in morphology and staining characteristics : Variations in morphology and staining characteristics have long been known in mycobacteria, and the leprosy bacillus is no exception. Morphological variations consist of the presence of short and stumpy forms, broken bacilli, cocoid forms with or without an attenuated rod projecting at one or both ends. Tinctorial variations consist of faintly staining bacilli resulting from decreased acid-fastness, and irregular staining resulting in the bacilli looking like diphtheroids.

Interpretation of tinctorial variations : Rees and Valentine (1962) had suggested that non-solidly stained leprosy bacilli were degenerated and non-viable. Rees (1969), and Shepard and McRae (1965) have taken the position that only solidly staining intact rods are viable leprosy bacilli. The other forms categorised as "non-solids", were considered "degenerate" and non-viable. Shepard and McRae (loc. cit.) and McRae and Shepard (1971) concluded from their experiments that the capacity to multiply in the mouse foot-pad was directly related to the capability of leprosy bacilli to stain solidly.

On the basis of this concept of the non-solidly staining forms being non-viable, a morphological index (MI) giving the percentage of solidly stained bacilli has been described. A lowering of this index is taken as a proof of therapeutic activity of a drug in a leprosy patient. The non-solidly staining bacilli or those which are lightly or irregularly stained, are considered by these workers to be degenerate and non-viable. Further, when there are no solidly stained bacilli in skin or nasal smears, the patient is considered to be non-infectious.

The matter is still highly controversial : While the utility of the morphological index (MI) for the purpose of assessing the activity of a drug is now generally well recognised, scepticism has often been expressed by several workers (including the present author) about *all* non-solid bacilli being non-viable.

It is a common experience with many leprologists that several active untreated lepromatous patients may show a very low, may be a zero MI. In this connection the WHO Panel on Therapy of Leprosy (1970) expressed doubts about the concept of *all* non-solidly staining forms being non-viable. The Panel remarked "It must however be borne in mind that non-solid bacilli may be seen without drugs having been administered. Indeed it has frequently been observed that untreated lepromatous patients show a morphological index varying from 0.50% to 50.0% even in fresh lesions of very recent origin. This observation has led some specialists to think that the concept of viable bacilli should be amplified to include forms that show slight irregularity of morphology or staining".

With reference to the morphological index reflecting the viability of the leprosy bacillus, the WHO Expert Committee on Leprosy in its fourth report (1970) observed : "Because of its limits of sensitivity, however, it is not a suitable procedure for distinguishing the infectious from the non-infectious patients, even when performed under optimal conditions by highly experienced investigators."

Chatterjee (1973) in an editorial in "Leprosy in India" has reviewed the subject. He states "the concept that viability in mycobacteria can be determined by its staining quality has always been a controversial issue. It is true that staining qualities vary in a mycobacterial population, and that it undoubtedly represents change in the biological character of the organisms. But, in the biological world, one always deals with grades of change, a spectrum, rather than an 'all or none' phenomenon." He thinks that the basic defect of the concept appears to be in the lumping up of *all* non-solid staining *M. leprae* as degenerate, and therefore non-viable and non-infective.

The Committee on Microbiology of the International Leprosy Congress, Bergen (1973) includes the following statement regarding the relation between morphology and viability of the leprosy bacillus. "The present MI does not distinguish the infectious from the non-infectious patients. No unified opinion has been formulated regarding the question whether the ratios of solid staining bacilli are associated with viability in the bacteriologic sense. Further studies appear necessary". This view has also been voiced even more strongly at the Second International Colloquium (1974) at Borstel in Germany. At this Colloquium, several speakers, including Karat, Ridley and Prof. Freerksen, clearly

stated that morphological and tinctorial changes in the lerposy bacillus cannot give information about its viability or non-viability. Karat remarked "In my experience there has been no consistent relationship between the number of solidly staining organisms present in a given biopsy homogenate and the cultivation of those bacilli in the foot-pads of mice." Ridley laid special emphasis on the fact that even slight variations in the staining technique would lead to differences in staining characters, and stated "That any index which depends on staining bacteria is notoriously open to difficulties." He further added that "it is obviously difficult to determine the exact point at which it ceases to be viable". Freerksen (1975 c) spoke of the environmental changes affecting the morphological and tinctorial characters of all mycobacteria including the leprosy bacillus. In this connection he stated "It is typical for all mycobacteria that by alteration of the medium they undergo considerable morphological changes interpreted as phenomenon of adaptation. When the chemotherapeutic substances are applied to an organism, the 'tissue medium' is rendered unfavourable for the growth of leprosy bacilli. The same thing happens when bacteria are transferred from one culture to another, or from one experimental animal to another. This phenomenon is not restricted to *Myco. leprae* ; it is common to all mycobacterial species we have studied with regard to this property." Earlier, while speaking on the Rifampicin-Isoprodian combination, he (Freerksen, 1975b) had referred to all species of mycobacteria having the ability to adapt to changing environmental conditions by granulation, fragmentation, etc. Therapeutic agents represent an environmental influence. On the other hand, under insufficient treatment, regular forms may recur. He goes on to say "that is why the decisive criterion is not the MI, but the reduction to zero of the BI."

The scepticism regarding all non-soldlly staining bacilli being non-viable is supported by the following observations.

Karat et al (1973) have reported the successful 'takes' in foot-pads of mice in 30 (83.4%) of the 36 experiments using zero morphological index AF bacilli from untreated leprosy patients. They have stated that while the reduction in morphological index in patients who had effective specific anti-leprosy therapy is an undisputable fact, where uncertainty arises is in the significance of these changes in the staining characteristic of *M. leprae* vis-a-vis their ability to multiply in the foot-pads in mice and to use this criterion for their viability.

Desikan (1976) at the Central Leprosy Teaching and Research Institute, Chingleput, while referring to the Morphological Index (the percentage of solidly stained bacilli), points out that slight alterations in the staining characteristics do not necessarily indicate non-viability of the bacilli. He had arrived at this conclusion by mouse-to-mouse passages of leprosy bacilli with different staining characters and morphological forms (solidly stained, the non-solidly stained bacilli of different forms—coccoid forms, broken bacilli, dumb-bell shaped bacilli, beaded bacilli, indented bacilli and short stumpy forms). He found that in 12 experiments with inocula containing 1-10% solidly staining bacilli, the rate of multiplication was the same as in the 8 experiments with the inocula containing non-solidly staining bacilli i.e. with the inocula with a morphological index of 0. This point was brought out most prominently in two experiments : the inoculum in one contained 97% broken bacilli and 3% beaded bacilli ; in the other case the inoculum contained only coccoid and highly fragmented bacilli ; all the same the multiplication was of the same order as in the case of other experiments including those with the inocula containing 1-10% of solidly stained bacilli. He concludes that his work does not support the hypothesis that fragmented bacilli are dead. He further says that after a particular stage these fragmented bacilli become non-viable but that "it would be difficult to state at what stage or at what time these fragmented bacilli are rendered non-living."

Conclusion

It can, therefore, be concluded that the question of *all* non-solid forms of the leprosy bacilli being degenerated and non-viable is still a very highly controversial matter, and that many workers are very sceptical about the alleged relationship between the staining characters of *M. leprae* and its viability. It cannot, therefore, be stated that when in patients under chemotherapy the MI from skin or nasal smears becomes zero, the patients become non-infective.

In view of the above statements, it is essential to take some steps to eliminate contact, especially of children, with infective patients under treatment till chances of their discharging bacilli whether solidly or non-solidly

stained through skin and nasal ulcers are eliminated, whether the case is early or advanced.

The writer believes that one of the most important loopholes in the leprosy control campaign through mass chemotherapy is that no steps are being taken in order to prevent the spread of the disease by patients under treatment, but who are still infective. There is no doubt that under effective treatment the bacillary load and therefore the infectivity of the patient gradually decreases, especially after the skin and nasal ulcers have healed and the nasal smears become negative. He believes that till this is achieved, some temporary steps should be taken to prevent contact between the infective patients and the healthy persons.

It is encouraging to note that the Government of India has now recognised the importance of this matter, and that some steps in this direction are being proposed to be included in the National Leprosy Control Programme. Let us hope that something subsstantial will be done in this matter. As regards the steps suitable to achieve this purpose, there appear to be three methods : (i) segregation at home, (ii) group segregation, and (iii) hospital segregation, in that order of priority.

(i) *Segregation at Home.* It may be said that 'home isolation' if effectively carried out, is the best method from the psychological, social and economic points of view. It is true that in most countries with a high prevalence of the disease, facilities for this purpose are at present not available in most homes. A separate room or hut, with separate feeding vessels, clothes, bed linen, towels, etc. are required for the purpose ; it may not be possible to afford these facilities because of the limited living space and limited resources of the family. It is therefore clear that, though possible in intelligent families with adequate resources, home isolation is not at present applicable on a wide scale in our country. However, every effort should be made to create conditions necessary for effective home isolation on a wide scale. Besides educating the people in this connection, necessary incentives should be provided for the purpose to the families which need help to practice this method. Home isolation should not mean that the patient should remain confined to his room or hut all the time. He should, on the other hand, be kept usefully employed in some work which does not bring him in contact with healthy persons. In villages it could be looking after the cattle, gardening and agriculture, etc. Of course, the treatment of the patients confined at home should be the responsibility of the mobile treatment unit working in that area.

(ii) *Temporary Stay at the Headquarters of a Control Unit.* When home isolation is not possible, or in case of destitute persons who have no home, it will be necessary to make some other arrangement for their temporary stay away from the healthy population till all skin and nasal ulcers are healed, and nasal smears become negative. Some arrangements may be made collectively for the patients in villages under one or more treatment units at the headquarters of a control unit.

(iii) *Temporary Hospitalisation.* If neither of the above two alternatives is possible, the patient may be temporarily hospitalised in general hospitals or infectious disease hospitals, and failing that in leprosy hospitals. Of course for the last course, the number of beds in the hospitals will have to be greatly increased especially at the Headquarters of the Leprosy Control Units in the field so that the patients do not have to go for hospitalisation far from their homes.

It should be borne in mind that, wherever they are kept, the restrictions are being put on them in the interest of the society, and that they should be provided with all necessary amenities of life.

(3) Need for Regular Treatment

It is generally known that all the detected cases do not register for treatment, and out of those who register a large percentage become irregular or drop out for one reason or another. Special efforts are therefore needed to keep all the registered patients attending regularly for treatment, in other words, for case-holding. Efforts in this direction are urgently needed not only for the sake of the individual but also for its effect on the general population, especially because irregular treatment, as of course also treatment with very small doses, is a potent cause of development of drug registance, the baneful effects of which for the general population have already been referred to in detail. The greatest risk to healthy persons exposed to infection from such cases is the appearance of primary i.e. pre-treatment dapsone resistance, which makes dapsone useless for them even at the start of

treatment. There are several measures that have been suggested by various persons to deal with this problem. The writer will make a mention of a few measures that appear very important to him.

(i) A sympathetic and helpful attitude on the part of the para-medical personnel. Through proper health education and repeatedly rubbing into them the advantages of regular treatment, the patients should be motivated to take regular treatment. It is also necessary for the workers to attend the treatment clinic punctually, and if for any reason the time and venue of a mobile clinic has to be changed, the patients should be informed about it sufficiently in advance.

(ii) Any specific reason for irregularity given by a patient should be carefully looked into and attempts should be made to remove their difficulties as far as possible.

(iii) The patient should be treated not for leprosy alone, but total health service should be rendered in case of minor ailments for which necessary facilities should be made available.

(iv) The para-medical workers should be able to spot early signs of 'threatened' and 'concealed' plantar ulcers, and should be able to teach the patients as to what to do when any such signs develop.

(v) The para-medical worker should carry out health education regarding the disease with the help of instructions given to him, and with the audio-visual publicity material supplied to him.

(vi) In order to enable the para medical workers to carry out the above stated functions, necessary changes should be made in their training, the period of which may have to be prolonged. Moreover, with additional duties assigned to them, their workload with regard to the number of population to be covered should be decreased.

(4) **Health Education—Need for strengthening it :**

The importance of health education has been recognised from the very start of the leprosy control programme, and emphasis on it has been given at nearly all the Leprosy Conferences/Congresses both National and International. However, in practice it has not received attention to the extent that is necessary. The advantages of health education are too well known and it is not necessary to deal with them here. It has also been agreed that the health education should be directed at all sections of the society, though the modes of approach will have to differ for the various sections. Some of the points regarding the methods of health education are referred to below.

(i) *Need for a qualified health educator.* For health education regarding leprosy to be put forcefully and correctly, there is need for some persons especially trained in the methods of health education. They should be made familiar with the various problems in leprosy to be tackled through health education, as also with the various aspects to be stressed in the health education regarding leprosy. Each state should have one or more such persons according to the needs of the individual states and according to the availability of suitable persons for the job.

Each Health Educator can visit periodically several centres by rotation, and in addition to working himself, can also train the staff of these centres who could carry on the work in between his visits to a particular centre.

(ii) The Health Educator and the staff responsible for carrying on the health education according to his directions should be supplied with adequate audio-visual material designed properly for carrying out the work satisfactorily.

(iii) The recent trend in certain quarters regarding health education is very disquieting. It should be clearly kept in mind that the health education should be based on PROVED SCIENTIFIC FACTS, although rendered in non-technical simple language. Of late it has been seen that several people are basing their health education on the possibilities on which investigations are still in progress. This relates to methods of transmission such as by talk, breath, etc. of the patients, through insect bites and the domestic flies, directly or by contaminating food or drinks. All these methods of transmission have been suggested and investigations regarding them are being carried on, but no investigator has proved or has claimed to have proved that infection does spread by such methods. They only speak of a possibility of these methods ; however, some enthusiastic workers take these methods as a certainty, and project it in their health education material. This tendency is very dangerous. If permitted to continue, it will undo all the work

that has been done for bringing about a change in the public outlook so that they adopt a rational attitude towards the disease and the persons suffering from it. The fear against leprosy that existed to a great extent till 20 or 30 years ago, and which is only slowly getting less, is likely to come back again, and this will undo whatever has been achieved by the health education till now. It may be stated to the credit of the Hind Kusht Nivaran Sangh Headquarters Office, Delhi that the health education material prepared by it is based only on proved scientific facts.

(5) Adequate Training in Leprosy of the entire Medical Profession

India has a huge leprosy problem. The National Leprosy Control Programme and the voluntary agencies are trying to solve this problem, but they alone cannot adequately deal with this huge problem. For this purpose it is necessary to involve all the medical profession. For this, four things are necessary :

(i) *Adequate training in leprosy at the under-graduate medical level.* The medical students at the under-graduate level should have adequate training in diagnosis, treatment and control of the disease. This matter is being discussed for a long time, and the attention of the Indian Medical Council has been invited several times to this urgent matter but so far without any tangible results.

(ii) *Orientation Courses in leprosy for general medical practitioners.* For the benefit of the general medical practitinoners, short orientation courses should be increasingly organised to keep them uptodate regarding the treatment and control of the disease.

(iii) *Refresher Courses for the medical (and para-medical) staff engaged in leprosy control work.* It is very essential to keep the workers abreast of the recent developments in the subject.

(iv) *Post-graduate Diploma Course in Leprosy.* The scope and knowledge in the field of leprosy has been so fastly expanding in the recent past that there is great need for instituting a post-graduate Diploma Course in Leprosy. The DVD course which is supposed to cover leprosy, cannot cope with the increasing knowledge about the disease.

(6) Protection of Healthy Children

Though leprosy may be acquired at any age, in countries where leprosy is highly endemic, most infections are acquired at early age, though the clinical manifestations of the disease may appear several years later. It is also well known that many children of infectious leprosy, if not removed from them, get infected, but that if removed from them soon after birth, they escape infection. Protection of the children of infective patients from being infected is therefore very important. For this purpose the following steps may be considered.

(i) *Separation of the child.* The best way would be to separate the children of infectious parents soon after birth, and to rear them at a place where they are not exposed to infection. The chances of the children escaping infection get much less with the length of time before they are separated, and early separation creates difficulties in feeding them, especially in tropical countries. This poses great difficulties unless some healthy relation is willing to adopt such healthy children. The other possibility is to keep them in institutions. However, children brought up in institutions specially meant for children of leprous parents suffer from great mental trauma and sitigma. If separation in an institution is found necessary, these children should not be kept in separate institutions meant for children of leprosy patients only, but in institutions or 'Homes' for taking care of children in general for any other reasons.

An alternate measure is to separate the infectious patients as indicated earlier.

(ii) *Efforts at making available a specific vaccine.* Because of the difficulty of separation of the children, especially soon after birth, it is necessary to think of other means for protecting such children. The ideal thing would have been to protect them by vaccination against leprosy as is done in relation to several other infectious diseases. However, as already stated, at present there is not available any protective vaccine against leprosy. Efforts in preparing such a vaccine are being vigorously followed, and it is possible that a vaccine may be available after some years.

In the absence of a prophylactic vaccine, the following measures can be recommended for protecting the contacts of leprosy patients.

(a) *Chemotherapy of leprosy patients on a mass scale.* Regular treatment of the source case with chemotherapeutic drugs, which in case of infective cases should mean treatment

with a combination of antileprosy drugs i.e. with multi-drug therapy. In the villages, due to intimate mixing of the people, the entire population of a village may be considered as contacts, and as such exposed to infection, and therefore at risk of infection. This would mean mass scale treatment of all leprosy cases, and that is the objective of National Leprosy Control Programme.

(b) *Prevention of contact with infective patients.* This matter has already been discussed, as also the means by which the object could be achieved.

(c) *Chemoprophylaxis.* In the absence of immunoprophylaxis, chemoprophylaxis with dapsone in small doses has been shown to have a great* protective value (Dharmendra et al 1965, 1967). In a controlled study using small doses of dapsone for prophylaxis carried out by the double blind method with a very large number of children upto 12 years of age of intra-familial contacts of lepromatous cases, these workers reported protection of over 52 per cent, provided the source cases were also treated with dapsone (DDS). They found that the protective value of dapsone was confined to the children upto 10 years of age. Therefore if children upto that age alone are considered, the percentage of protection worked out to be much higher. The value of chemoprophylaxis has been confirmed by several other workers in different parts of the world.

The prophylactic doses of DDS. Although larger doses for prophylaxis were used in the original studies, in view of later experience the following prophylactic doses of DDS are recommended for child contacts according to age.

Age group in years	Dose in mg	
	If given twice a week	If given once a week
0 — 2	5	10
3 — 5	10	20
6 — 10	25	50
Over 10	50	100

In case of the child who is in contact with a lepromatous mother, who is under regular DDS therapy, there is no need for prophylaxis till the child is weaned, because the breast fed child will get adequate amounts of DDS from the breast milk.

The duration of prophylactic treatment. The duration of prophylactic treatment should be for 3 years after the source case becomes non-infective, or is removed from contact with the child, or if the child is separated from the source case. Of course, as stated earlier, it has to be emphasized that prophylactic treatment of a contact should be in addition to the treatment of the source case.

It may be stated that there is no danger of development of sulphone resistance as a result of chemoprophylaxis. In multi-bacillary (lepromatous and near lepromatous) cases of leprosy, use of very small doses of dapsone tends to produce resistance to the drug. However, that risk does not apply to healthy contacts, who if infected are likely to harbour only very small number of bacilli.

(iv) *Methods of family planning.* Another method of minimising this problem of children is to advise the patients to practice methods of family planning, as is being done in case of the general public in order to check the progressively growing population of the country at a very fast rate. However, the question of compulsory sterilisation of leprosy patients should not be thought of, and no quarter should be given to enact any legislation to this effect as is sometimes proposed. Any legislative measure in this matter will serve no useful purpose but may do definite harm. Attempts at compulsory sterilisation in this matter will lead to concealment of the disease, whereas there is urgent need to detect cases of this disease at an early stage, and to treat them to prevent advancement of the disease and deformities. Moreover, the patients may become hostile, and may not co-operate with other activities of the Leprosy Control Programme. Moreover, it should be appreciated that even if compulsory sterilisation of all leprosy patients were possible, the measure will not have an appreciable impression on the spread of the disease, since a vast majority of new cases occur amongst children of healthy persons through extra-familial contact. Of course, the incidence of the disease is much higher in the intrafamilial than in the extra-familial contacts, but the overall situation is reversed because of the extra-familial contacts being overwhelmingly greater in number.

Indications for sterilisation. There are two main indications for this measure (a) Prevention of spread of infection to the children, i.e.

* Going by published results, 'great' seems to be a bit of over-statement-Editor.

on public health grounds and (b) Prevention of strain of pregnancy and lactation to the mother, i.e. on medical grounds.

(a) *As a preventive measure*, it is indicated when one or both of the parents are cases of leprosy of the infective type ; or when living conditions of the patients are such that children born of even non-infective cases are likely to be exposed to infection from other infective cases, for example, in settlements of beggers with leprosy.

(b) *On medical and social grounds* it may be indicated in some non-infective cases of leprosy, or in a non-leprous male partner when the wife is suffering from non-infective leprosy, to save her from the strain of pregnancy which may affect the disease adversely.

Someo ther methods of restricting birth of children. At the present moment the need for family planning, and of restricting the number of births is receiving great attention in order to prevent further explosion of population. There are several new contraceptive methods meant for the population in general ; these methods should also be made use of in the case of leprosy patients. The most useful and practical contraceptive methods appear to be the simple surgical measure of vasectomy or the use of the condome by the male partner ; and surgical method of tubectomy or an intra-uterine loop for the female partner. The oral contraceptives are also being advocated, and there is also the possibility of developing an anti-pregnancy vaccine.

(7) Role of Leprosy Hospitals

Mass Scale Chemotherapy is the Ideal Approach, for Leprosy Control. Till the discovery of the sulphones for the treatment of leprosy, the ideal method of control of the disease was considered to be the isolation of infective cases of this disease, and this was impracticable on a large scale. The sulphones brought about a revolution not only in the treatment, but also in the methods of control of the disease. The present day anti-leprosy campaigns are therefore mainly based on the mass scale treatment of the cases with sulphones and/or other chemotherapeutic drugs discovered after the sulphones. This, of course, is undoubtedly the right approach to the problem, and the only approach possible especially in countries with huge leprosy problems. However, the limitations of sulphones alone has already been indicated, as also the reasons for the multi-drug therapy for multi-bacillary (lepromatous and near lepromatous) cases.

Short Term and Selective Hospitalisation is Still Necessary. Although wide scale chemotherapy on an outpatient basis is in general the ideal method for the control of leprosy, short term and discriminate hospitalisation on a voluntary basis is still needed to supplement the mass scale outpatient chemotherapy to meet certain situations. A reference has already been made to the need of this method in the highly infective cases, contact with whom cannot be eliminated by other methods such as segregation at home. Hospitalisation is needed for certain other reasons also as discussed hereafter. It may be stated that to switch over from hospitalisation, which was the only method practiced before sulphone therapy, completely and exclusively to mass scale chemotherapy is moving from one extreme i.e. only hospitalisation to the other extreme i.e. only out-patient mass scale therapy, is not a right move. While mass scale chemotherapy on out-patient or domicilary basis is the method to be preferred in general, the need for short term and selective hospitalisation should not be altogether ignored. The role of such hospitalisation should be recognised, and a balanced view in the matter should be adopted.

Need for Selective and Short Term Hospitalisation. Short term hospitalisation may be necessary for more than one reason, and adequate arrangements should be made to meet the needs. Facilities for hospitalisation will be necessary in the field in association with Leprosy Control Unit, at the district level (in general and teaching hospitals, or failing that in a separate leprosy hospital), and in association with leprosy institutes in which leprosy research is in progress.

The various purposes for Hospitalisation. Short term and discriminate hospitalisation may become necessary for the following reasons :

(i) *As a Public Health Measure.* This has already been referred to. Hospitalisation on this account will be necessary in case of highly infective cases, whether early or advanced, till they cease to discharge leprosy bacilli (whether solidly or non-solidly stained). Of course the need for hospitalisation will arise only in those cases where 'home' or 'group' isolation is not practicable.

It is encouraging to note that the Government of India has accepted the principle of

providing facilities for lodging such cases at the Headquarters of each Leprosy Control Unit. However, the financial assistance proposed to be given for each patient's maintenance, as also for supporting his family is very meagre, bare sum of Rs. 40/- per month. The patient is expected to supplement this amount by earning through doing some work. It is wondered what work can they do during their short stay ; the only work they could do would be to resort to begging, which is a most undesirable thing.

(ii) *Treatment of Acute Complications.* The acute condition may be due to leprosy, for example severe 'reactions', acute neuritis, eye or nose complications, etc.

(iii) *Treatment of patients with some chronic condition.* The chronic conditions for which hospitalisation is necessary include chronic (progressive) reactions in lepromatous cases, complicated neuropathic ulcers, fixed deformities of upper and/or lower limbs, nasal deformities, difficult cases not responding to the usual lines of treatment, etc.

It is gratifying to note that the Government of India has accepted the principle of making available beds for treatment of acute and chronic complications in teaching and general district hospitals. However, it is essential that beds for the treatment of acute complications should be provided at the Headquarters of each Leprosy Control Unit also. In very severe acute conditions, the transport of the patient to a distant hospital creates problems which may cause delay even at the risk of patients life.

(iv) *Treatment of Acute Complication due to other diseases.* Leprosy patients are as likely to get acute complications caused by other diseases, for example acute abdomen etc. These patients should normally be able to get admission in a general hospital for treatment of the acute condition. However, it often happens that because of their having leprosy, they are often not admitted into general hospitals. Efforts should no doubt be made to change the attitude of the doctors incharge of the hospitals. However, till this change can be brought about, leprosy patients with acute complications caused by other diseases should be admitted temporarily in leprosy hospitals for the treatment of the acute condition. The same may apply to maternity cases, especially the complicated ones.

(v) *For teaching at the Medical Colleges.* In countries where leprosy is endemic, adequate teaching for the diagnosis and treatment of leprosy should be an essential part of teaching at the undergraduate level. The teaching should not be merely theoretical, but should include demonstration of the various types of leprosy lessions, and of the complications and sequelae of the disease. For this purpose it is essential to have a ward for leprosy in the teaching hospital so that adequate material is available for necessary demonstrations to the students.

(vi) *Research in various aspects of leprosy.* Researches in various aspects of leprosy are being undertaken on a progressively increasing scale by workers in various disciplines of science. Some lines of research can be followed without leprosy patients being present nearby. However, in case of some studies, it is essential that patients be available nearby to be kept under observation. Such research projects include :

(a) Clinical trials of new drugs found useful for the treatment of leprosy by experimental chemotherapy.

(b) Studies on cases getting relapses due to drug resistance (while the patient is still under treatment with a drug) or due to persistence of drug sensitive bacilli (when the treatment is withdrawn after it has been administered for a long time—over 10 years or more).

(vii) *For training personnel needed for Leprosy Control Programme.* Various kinds of personnel engaged or to be engaged in the leprosy control programme have to be trained for carrying out their duties efficiently in the field. Such personnel may be medical officers, para-medical workers, physiotherapy technicians, occupational therapy technicians, social workers, health and laboratory assistants, nurses, etc. For proper training of such personnel it is essential to have leprosy hospitals or institutions which have facilities not only for training in clinical and laboratory (bacteriological examination) techniques but also have facilities for training them in the field. These hospitals or institutions will also have to arrange for refresher courses for keeping the workers upto date in their respective fields.

THE PROPER USE OF HOSPITALS. While advocating the importance of hospitals in a Leprosy Control Programme, it is necessary to point out that they should not revert

to fulfil the same functions that they were supposed to serve in the past. They should be used only for specific prurposes as stated above, or for any other legitimate function for furthering the cause of controlling the spread of leprosy.

In this context it may be stated that the hospitals advocated here should not be used for committing vagabond leprosy patients under any existing or future legislation. They should not also be used for long or permanent stay of any other category of leprosy patients.

There is certainly great need for taking care of crippled patients, but the hospitals visualised here are not the proper place for this purpose. To meet this particular situation, the right kind of institute should be of the nature of a 'Poor Home' or 'Asylum'.

SUMMARY

1. The various activities under the Leprosy Control Programmes have been briefly considered.

2. The impact of the Programme on Controlling the spread of the disease has been examined. It has been concluded that although a large number of individual patients have benefitted by it, the programme has not made an appreciable impact on decreasing leprosy except in a few small countries or in limited areas of a country. This is true not only for India, but also for other endemic countries in the world. Thus the enthusiasm and optimism aroused at the commencement of the Dapsone-Based Control Programme have not been realised.

3. Certain developments in chemotherapy (for example development of dapsone-resistance to a progressively increasing extent) indicate that if the programme is continued as upto present, one cannot look forward to the control of the disease for a long time.

4. To achieve the desired objective, besides plugging the loopholes in the administrative set up, there is need for changing our view point regarding several matters.

5. The important points in which change in outlook is needed are discussed. It is admitted that there may be several other points needing attention.

6. The points to which attention has been invited in the present paper are :

(i) The need for developing inexpensive multidrug therapy for lepromatous and near lepromatous cases, which could be applied in developing countries in which exists the present day leprosy problem.

(ii) The need is stressed for eliminating contact with infectious patients under treatment till they cease to discharge leprosy bacilli (solidly stained as well as non-solidly stained). The possible measures for this are discussed.

(iii) The need for ensuring early and regular treatment is emphasised, and some of the means are discussed.

(iv) The need is stressed for strengthening the Health Education regarding the disease, and some suggestions for the same are made. The danger of basing health education on theories, and not on proved scientific facts, is highlighted.

(v) The need for involving the entire medical profession in the programme is indicated, and for this purpose the urgent need of giving adequate education in leprosy at the under-graduate medical level is emphasised.

(vi) The special need for attention to the important problem of children is emphasised, and some means for achieving the purpose are indicated.

(vii) The important role that hospitals can play, in supplementing the wide-scale chemotherapy on out-patient or domiciliary basis, has been emphasised. Some of the ways in which hospitals can help the Leprosy Control Programme have been indicated. There may be some other directions in which the hospitals can be helpful, but a note of caution has been added that the hospitals should not revert to their old role, and they should not be used for admitting patients committed under any existing or future legal measure. Neither should the hospitals be used for admitting crippled patients, for whom there should exist separate arrangements.

7. Improvement in socio-economic and hygienic standards of the general population, although not specifically an antileprosy measure, will contribute greatly towards control of leprosy as also of other infectious diseases.

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"RELEASE FROM CONTROL" IN LEPROSY

T. F. DAVEY

Up till 10 years ago the "criteria for discharge" in leprosy were regarded as a logical, necessary and relatively clear cut aspect of patient care. The menacing psychological atmosphere which surrounded leprosy, both for patient and doctor alike, gave enormous importance to the concept of an end point, when after prescribed courses of chemotherapy, and the attainment of a condition of "inactivity", a further period of observation and treatment could lead to the day when the disease could be regarded as arrested, and, hopefully, overcome. At that point chemotherapy could be suspended, a medical certificate given, and with the safeguard of regular but occasional follow up, the patient could be restored to normal life. This was a day of great emotional content for patients.

During the past decade several aspects of this approach to leprosy have been challenged by events and by better understanding of the bacteriology and immunology of *Mycobacterium leprae.* The idea that a line can be drawn between infection and no infection has been rudely shattered. The very natural bacillus orientated approach made it easy to pontificate and even legislate on behalf of patients in the belief that they would meekly follow our advice. We have had to learn that the final arbiter on how much chemotherapy is taken and when treatment is stopped is not the doctor, but the patient himself. All our well laid plans and carefully considered judgments fall to the ground if the patient on whose behalf they are made simply fails to co-operate. He, as well as the germ, must be at the centre of our concern, and our approach be such that our well meant programmes are not frustrated.

The judgments of the WHO Expert Committee on Leprosy on this subject are highly relevant. The Report of the 4th Expert Committee (1970) included the following:

"A leprosy patient without any sign of clinical activity, and with negative bacteriological findings should be considered as an "inactive case".

Once inactivity is achieved, *regular treatment* should be continued for varying periods of time before a patient is "released from control" (rfc).

These periods should be 1½ years for tuberculoid, 3 years for indeterminate, and at least 10 years for lepromatous and borderline cases. Since data on relapse after rfc are scarce, it is advisable and important to continue the follow up of lepromatous cases but without treatment. Some leprologists consider that this should be done for life".

This statement was endorsed by the 5th Expert Committee (1976) with an interesting proviso. "The Committee strongly recommended that inactive tuberculoid and indeterminate cases be promptly released when they meet the criteria. This action is not only in the interest of the patient but has an important bearing on operational efficiency and would release resources for other activities of the programme".

Clearly in 1976 wider issues came within the purview of the Committee than the earlier approach, but the endorsement of the 1970 statement means that the views then expressed are carried forward as the recommended norm for today. Some aspects of this invite discussion.

It must first be said that for patients with types of leprosy towards the tuberuloid end of the spectrum the traditional approach remains valid. With such patients the question of ostracism and isolation should not have arisen, and following chemotherapy, inactivity and continuing therapy for the times suggested by the Committee, an end point can be envisaged and a discharge certificate be given with minimal prospect of relapse. The key here is surely the existence of cell mediated immunity as the limiting factor in

the infection, holding the promise of continuing ability to deal with the bacillus, and monitored by a positive reaction to lepromin, whether this was there from the start or develops in association with reversal reactions.

CONTINUING CHEMOTHERAPY AND SURVEILLANCE.

When we turn to patients with bacilliferous leprosy the position is rendered much more difficult by the discovery that even in spite of long periods of chemotherapy viable *M. leprae* may persist in internal organs, notably bone marrow, lymph glands and nerves. Clearly it is very important that the types of patient in whom such persister bacilli are found should be identified as accurately as possible. At present they must be assumed to include all patients with established lepromatous leprosy. How far this phenomenon extends into the borderline part of the spectrum remains to be determined. The crucial question is the extent to which such persister bacilli are responsible for relapse. A lot more data are needed on the whole subject, but there seems to be no logical reason why persister bacilli, granted favourable conditions, should not recommence reproductive life, the only possible exception being the small minority of such patients who ultimately attain lepromin positivity.

It is not difficult to envisage such favourable conditions. We already encounter them in relation to downgrading reactions. Clearly the discovery of persister bacilli has an important bearing on chemotherapy. With such patients there can surely be no magical moment when after 10 years of inactivity we can say, Now it is all over, you can stop taking dapsone. At present the only defence we have against relapse is continuous chemotherapy. As long as we are dependent on dapsone for maintenance therapy it would seem to be obvious advice to the patient with LL or BL leprosy that he should continue to take dapsone at therapeutic dosage indefinitely, even though he appears to be clinically inactive. This means that in present circumstances there should be no discharge from treatment for such patients, and the "criteria for discharge" have become irrelevant.

By the same token there can be no discharge from regular surveillance. The whole purpose of surveillance is to monitor the possibility of relapse, whether this is caused by dapsone sensitive or dapsone resistant bacilli. As long as we accept the reasonable possibility of relapse, then surveillance must contiue indefinitely, and is indeed very important.

It would appear therefore that in LL and BL leprosy, with present chemotherapy and with present day knowledge, discharge from treatment or from surveillance should not be advised, both in the best interests of the patient and of the community.

THE PERSONAL FACTOR

Acceptance of this principle immediately poses a difficult question. How can we expect the cooperation of patients in such procedures? Careful studies in recent years have indeed exposed the truth that frequently only a minority of patients continue to take dapsone as prescribed (e.g. *Malawi;* Ellard, Gammon and Harris (1974); *Ethiopia,* Low and Pearson, (1974); *Bombay,* Naik (1977). The same applies to attendances at treatment clinics. Many patients after longer or shorter periods of attendance simply discharge themselves and make nonsense of the medical criteria for discharge. It so happens that patients with LL and BL leprosy are often the most faithful in their attendance, but there is a problem here which must be resolved.

Now it is a fact of medical experience that people in general like to take medicines, whether they are Africans, Asians or Europeans, and will continue to do this as long as they feel that prescribed medicines are doing them good, the medicines are easy to obtain, and there are no economic or social problems involved. The taking of tablets indefintely holds no intrinsic problem. Millions of people do it, e.g. for hypertension, rheumatic conditions, or diabetes. Exactly the same is true of periodic medical examinations, provided the doctor—patient relationship is what it ought to be. Why then do we expect something different where leprosy is concerned? The reason cannot lie simply in the need for protracted treatment. It lies in the way the patient regards his illness and in the way he feels that other people, including the doctor, regard him, the sufferer from leprosy. All too often in the minds of patient, community and doctor alike, leprosy continues to hold a special anxiety-creating position, the natural reaction to which is to turn away from it, fail to face it, or forget it as quickly as possible.

The WHO Committee recommends 10 years of chemotherapy after inactivity in bacilliferous leprosy. If a patient has persisted for 10 years, he must also have got

into the habit that there should not be the slightest difficulty in his taking it for 11,12 years or indeed indefinitely. This is not the problem. The real problem is the desire to escape from the association with leprosy. This is something that deserves much more careful consideration than is usually given to it.

The best likelihood of maintaining continuity of treatment and surveillance, of encouraging the patient to persevere, will occur if three things are safeguarded.

1. The patient must be helped to understand the nature of his illness.
2. The doctor—patient relationship must be good. So much depends on this. It is the experience of the writer that where patients believe they are going to be welcomed and treated with understanding and consideration they are prepared to face the facts of their disease and respond with continuous cooperation.
3. Dapsone must be available as simply and unobtrusively as possible, *not* in the context of time consuming frequent visits to special clinics labelled in everyone's minds as reserved for people with active leprosy.

These principles apply during the first 10 years as well as subsequently. If they can be achieved there seems to be no logical reason why a patient should not of his own choice, continue to remain under chemotherapy and surveillance indefinitely.

It appears to the writer that the sustained cooperation of patients with LL and BL leprosy is made unnecessarily difficult by the perpetuation of old ideas and emphases.

The WHO definition of inactivity includes *negative bacteriological findings,* a feature which condemns many patients at the lepromatous end of the spectrum to long years of carrying the anxiety, and usually the stigma, of active leprosy. The traditional attitude would maintain that as long as acid fast material, regardless of its morphology, is found in routine skin smears, the patient is still suffering from active disease, and by inference other people are at risk.

Ever since the work of Rees and Valentine (1962), the judgment has continuously built up at centres of the highest excellence in leprosy research, that viability in M. leprae is associated with the intact rod shaped, uniformly staining organism. Various attempts have been made to cultivate *M. leprae* from fragmented bacillary material. None has been authenticated.

If we are ready to accept that it is the morphologically intact normal staining form of the bacillus which is responsible for th disease leprosy and for transmitting that disease, then any basic anxiety we have concerning leprosy *as a transmissible disease* should centre around that form of the bacillus and not around dead fragmented forms of no significance in the transmission of the disease. The role of dead bacilli in relation to ENL and neurological aspects of leprosy is an important but quite different question. From the angle of the patient's capacity to transmit the disease, can it not be generally accepted that if the morphological index is zero, i.e. no bacilli of intact shape and staining can be found on careful bacteriological examination, then that patient is not to be considered as infective to others. Persister bacilli in deep organs are not capable of leaving the body and have no relevance to this matter. The important point is that if the patient is in practice regarded as not infective to others, then we should say so. This would give an enormous boost to the morale of patients with these types of leprosy. So often the consciousness of being infective to others creates deep anxiety in the minds of patients where their children are concerned, and is a potent factor in the depression that so easily leads to despair and non-co-operation. Furthermore, the logic of the situation should be followed through. The patient should surely be regarded as in no way different from any other sick person. He should be able to attend general out-patient's departments, occupy any appropriate hospital bed, be employed in any suitable capacity and have no social restrictions placed on him whatever. The idea that these normal prerogatives of people in community are to be denied until the traditional routine smears are totally negative for any acid fast material is scientifically unsound and indeed may be considened uncharitable. This suggestion is not inherent in the WHO statement, but it is very much the common interpretation of what "release from control" really means, an echo of earlier rigid attitudes to this disease.

A LIBERAL OUTLOOK MUST BE BACKED BY SOUND TECHNOLOGY

If we are looking diligently for viable bacilli, our technology must be reliable. This means first, that the nose must be included in our attention. This is still frequently neglected,

or if included, nasal examination often takes the form of old fashioned septal smears, taken less than 2 cms within the anterior nares and calculated to yield nothing important. The inferior turbinate must engage our attention, and if as frequently happens it does not seem at first glance to be there, we need to realise that its anterior end has already been eroded by serious lepromatous disease. A bacteriological examination of the nasal discharge, choosing saneo-purulent areas is a sine qua non.

Secondly, relapse commonly first manifests itself by the appearance at may be a single site in the skin of large numbers of normal staining bacilli in a patient elsewhere and previously exhibiting only fragmented bacilli. Three months later normal viable bacilli are likely to be widespread, but by then it is certain that intranasal infection will have been re-activated, may be worse than before initial treatment, and the patient be already discharging large numbers of viable bacilli from the nose. Early discovery of relapse is thus extremely important. There is no guarantee that common methods of skin smears, selecting fixed sites in an inflexible routine, will identify relapse in its earliest stages, though careful clinical examination might well have aroused suspicion. This is particularly important if the relapse as is very common, takes the form of histoid lesions. An important feature of histoid leprosy is its capacity to appear in areas of the body not usually selected for routine bacteriological examination, e.g. the buttocks, lower abdomen, upper thighs and genitalia. Histoid lesions readily ulcerate and discharge enormous numbers of viable bacilli. To the uninitiated a well defined histoid lesion might even be mistaken for a reversal reaction or unusual form of ENL. Clinical acumen and skill in taking and reading smears are essential if relapse is to be detected early. Failure on either side brings surveillance into disrepute and leads to the pessimistic dictum that inactivity in lepromatous leprosy cannot be accurately assessed by routine bacteriological methods. There is comfort in the fact that relapse is far more common among patients who are not taking regular chemotherapy than among those who are, and this particularly applies to relapse with histoid leprosy.

WIDER ISSUES

In all our judgments affecting the life and well being of patients, the preservation and protection of the patient's place in community life is a long term priority and there is no escape from our responsibility in this direction. Some separation during the stage of the disease when the patient is discharging viable bacilli must be acceptable, but as the morphological index is usually zero within 6 months or thereabouts of starting treatment this is the sort of limit that needs generally to be visualised. There is of course no harm in some sort of "disease arrested" certificate following the criteria enunciated by the WHO Committee, but far more important in practice for the patient with LL or BL leprosy would be some form of medical certification given on request when the stage of negative MI had been attained, and indicating that the patient could be regarded as non-infective to others. Such a certificate would indeed release the patient from his primary anxieties and restrictions, encourage his continuing cooperation and promote a much more open and healthy attitude to leprosy generally.

It must be admitted that to secure such conditions considerable re-orientation and re-education of both patients and the community are needed, regarding the nature of leprosy, the delivery of chemotherapy, and the meaning of surveillance. It can however be done, as Antia (1977) has shown.

The fear that leprosy may be transmitted by forms of the bacillus other than the intact rod shaped bacillus may be hypothetical, but it dies hard, especially in relation to leprosy that appears to have been traced to patients considered bacteriologically negative. Recent work by Desikan (1977) showing that viable *M. leprae* may persist after dessication for up to 11 days has a direct bearing on this, and pinpoints possible unsuspected sources of such infections. The basic plea of this paper is that our sense of responsibility for patients with LL and BL leprosy should help us to accept with courage the facts regarding the viability of *M. leprae* which have been authenticated, and apply them resolutely.

There is one final point. Is "Release from Control" a phrase worth retaining in its present context? In common English usage "release" suggests a previous state of bondage or imprisonment. "Control" suggests a restriction on movement. Both words, used in relation to patients who have been under chemotherapy for years and exhibited no sign of viable bacilli for a long time are not only irrelevant but psychologically harmful to patients, workers, and community alike. Are they really necessary?

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Anknowledgement

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BCG VACCINATION IN THE PROPHYLAXIS OF LEPROSY

L. M. BECHELLI

In 1939, studying the correlation between the lepromin and tuberculin tests in Paris, Fernandez observed a high proportion of lepromin reactors (Mitsuda reaction). This reactivity was ascribed to a cross-sensitization to *Myco. tuberculosis,* because the tested individuals presented a positive Mantoux reaction and lived in an area where leprosy was not endemic. In the light of these findings, Fernandez tried to determine whether the administration of BCG vaccine would cause the conversion of Mitsuda reaction in individuals non-reactors to lepromin.

He administered BCG to 123 children with negative tuberculin and lepromin. One month later all but one had a positive Mitsuda reaction. The lepromin test was repeated and the results were as follows:

87 (70.73 per cent) presented a positive Mitsuda reaction (Nodule or papule of 5 mm or more, 21 days' reading);

26 (21.13 per cent) had a slightly positive reaction (induration larger than 3 mm and less than 5 mm), and

10 (8.13 per cent) had not reacted.

Fernandez referred to the "possibility of awakening, in healthy people, a resistance against Hansen bacilli by the BCG vaccination". This possibility should be investigated especially in contacts, and if results were confirmed a preventive agent of great value could then be used.

The existence of a cross-sensitization between tuberculosis and leprosy had already been admitted by Cummins and Williams (1934).

After Fernandez's report increasing attention was focused on the subject, which became one of the most important in leprology, due to its eventual implications for leprosy control. If the studies, mainly field epidemiological trials, indicated a preventive effect of BCG vaccination against leprosy, the methodology of control could be substantially changed and better results would be achieved in preventing the spread of the disease.

We shall consider initially (A) the immuno-allergic correlation between tuberculosis and leprosy by the comparative study of tuberculin and lepromin tests; (B) the effect of BCG vaccination on the lepromin reaction and finally, (C) epidemiological studies and field controlled trials.

A. Immuno-allergic correlation between tuberculosis and leprosy by the comparative study of tuberculin and lepromin tests*

Investigation of the immuno-allergic correlation between tuberculosis and leprosy has been almost exclusively undertaken to obtain evidence of a cross-sensitization between tuberculosis and leprosy. This has been done by the comparative study of the tuberculin and lepromin tests and by the effect of BCG vaccination on the lepromin reaction.

Comparative study between the tuberculin test (Mantoux reaction) and late lepromin (Mitsuda) reaction

In a review of the subject, Bechelli (1962, 1970 and 1971) studied the co-efficient of correlation of tuberculin and lepromin positivity in different areas or countries; the late lepromin reaction in healthy individuals with negative or positive tuberculin tests; tuber-

* A detailed review of the literature can be found in Bechelli, L. M. (1971), *Acta Leprologica, 42-43*, 63-125. In this paper, the relevent references for the author mentioned in the text, may be found.

culin and late lepromin reactions in leprosy and tuberculosis patients. In the light of the data reviewed, and of his own personal studies, he drew the following conclusions:

— In many of the groups studied tuberculin positivity is associated with a higher proportion of positive Mitsuda reactions. This excess of lepromin reactors among the tuberculin-positive people has been attributed to a cross-sensitization with *Myco. tuberculosis* or some germ related antigenically with it.

— Among the tuberculin-positive people there is a variation of the proportion of lepromin positivity and of lepromin reactors from one area to another, and even in the same area. This seems to reduce the importance of cross-sensitization with *Myco. tuberculosis* and imply the existence of other more important determining factors of lepromin positivity.

— The proportion of lepromin positivity in tuberculin-negative people (96,7 per cent in a group of contacts) is high.

— Among the tuberculin-positive individuals a variable proportion—often similar to that of the negatives and sometimes high as in the data of Davey et al. (1958)—do not react with lepromin.

— In lepromatous patients, tuberculin-positive or negative, the Mitsuda reaction is usually negative.

— Tuberculin positivity in tuberculosis patients may or may not be associated with a higher proportion of lepromin reactors.

— The appraisal of the data reported leads one to admit the existance of a cross-sensitization with *Myco. tuberculosis,* but within certain limits which seem to be narrow.

Further studies are necessary, especially in rural areas and in children 0-4 years old, in endemic and non-endemic areas, including also tests with other acid-fast mycobacteria.

Comparative study between the tuberculin test (Mantoux reaction) and early lepromin (Fernandez) reaction

Some authors think that the results suggest a group sensibilization while others admit that cross-sensitization would occur inconstantly and within a limited range.

B. Effect of BCG vaccination on the lepromin reaction

1. BCG and lepromin reaction in healthy individuals

Many investigations were carried out in different parts of the world and the main data were assembled in a table in Bechelli's paper (1970) and (1971). The chief aim was to determine the proportion of lepromin conversion after BCG vaccination. The methodology of this study was usually as follows: in the first phase of the experiment the lepromin test was performed in a group of healthy people, contacts or not. After reading the late (Mitsuda) reaction (21 to 30 days later), the lepromin negative individuals were vaccinated with one or more doses of BCG. However, this type of investigation has a bias, i.e. the possibility that the preliminary lepromin injection could interfere with the results in subsequent tests. In view of this, the Committee of Immunology of the VII International Congress of Leprology (1959) considered a preliminary test with lepromin not necessary, and suggested a new methodology; "with two comparable and sufficiently large groups of subjects, BCG may be given to one group, with lepromin testing afterwords, but the controls would be tested with lepromin only once, to establish the rate of "natural" lepromin reactivity of the population employed". Other recommendations on this matter were also made by a committee in the Symposium on the use of BCG in the prevention of leprosy, Rio de Janeiro (1957).

It should also be emphasized that in the majority of investigations control groups were not included in the trials.

It was seen that the lepromin conversion occurred in a high proportion of vaccinated people, around 80 per cent, and even 100 per cent in some reports. On the other hand, some authors have observed it in a relatively low proportion, between 40 and 50 per cent. These results were obtained by oral or intradermal BCG. The difference in results might be attributed to many factors: lepromin test (bacillary content and reading criteria), doses and validity of BCG, interval between vaccination and lepromin testing, age-groups of persons studied.

Azulay (1948), Rosemberg, Souza Campos & Aun [1951 (a & b) and 1952] did not report lepromin conversion in any case in the control group. However, Paula Soza, Ferraz &

Bechelli [1953 (a)] Paula Souza et al. (1953 and 1956), Bechelli, Quagliato & Nassif (1953) observed frequent lepromin conversion in the control group after re-testing, between 44 per cent and 80 per cent. In 21 non-vaccinated children who underwent four lepromin tests at intervals of about three months, Rosemberg et al. (1960), observed 43 per cent of lepromin conversion, which reached 90 per cent in 20 children BCG-vaccinated orally with three weekly doses of 0.10 g and 0.20 g. Lepromin conversion in the control group was also reported by Chaussinand (1948), Silva, Rabello Neto & Castro (1956), Doull, Guinto & Mabalay (1957).

The lepromin conversion attributable to BCG would be the total positive reactions less the proportion of lepromin positivity in the control group. In fact, according to Doull, Guinto & Mabalay (1957), besides BCG, other causes play a substantial part in inducing reactivity to lepromin, i.e. natural causes and lepromin. The importance of the latter in the investigation on BCG had been emphasized by Paula Souza et al. and by Ignacio, Palafox & Jose (1955).

Since the proportion of lepromin positivity is very low in 0-4 year old children, and then increases with age to reach about 80 per cent or more in young adults, it would be expected that a large difference would be seen between the vaccinated and control in children 0-4 years old, while after that age the difference would gradually decrease, and then the lepromin conversion would be similar in both groups. Therefore, it appeared that it was in the 0-4 age-group (and particularly the 0-1) that the BCG-induced lepromin positivity could be best checked. Consequently, the investigation carried on in this age-group should especially be taken into account. Rosemberg, Souza Campos & Aun (1950, 1951 and 1952) and Rosemberg et al. (1960), in several groups of children reported from 90-100 per cent of lepromin conversion. Bechelli (1958) in 0-1 year old children observed 45 per cent in one group studied and 41.7 per cent in another, but the difference from the control group was not significant, though showing a tendency to an influence by BCG vaccination.

In a group of 550 children, 6 to 35 months of age, Doull, Guinto & Mabalay (1957) estimated with regard to the proportion of all children becoming reactive from each cause, as follows: from natural causes 11.5 per cent; from the lepromin test 7.2 per cent; from BCG vaccination 33.4 per cent (highly significant). "The conclusion is reached that increase in frequency of reactivity to lepromin in persons vaccinated with BCG cannot be attributed to the vaccination alone. If no preliminary test is given, natural causes will contribute; if a preliminary lepromin test is given, both natural causes and the test". They also stated: "If the differences between vaccinated and control groups in the present experiment represent the correct picture, the effectiveness of BCG is much less than is commonly supposed".

Souza Campos et al. (1962) reported that among tuberculin-negative children of 6 to 34 months of age, the frequency and intensity of the lepromin reaction was significantly greater in those BCG vaccinated than in the non-vaccinated. The intensity of the reaction did not differ significantly when BCG was administered intradermally or orally. However, with increasing age, children receiving oral BCG showed a significant decrease in the proportion of lepromin reactors. It was also reported that in children not receiving BCG—either in the control group or among those inoculated with lepromin—the intensity of the reaction increased significantly with age.

With regard to the positivity of the early (Fernandez) reaction after the BCG vaccination, the following results were reported: Azulay (1949) 66.7 per cent, Rosemberg, Souza Campos & Aun [1950 (b) and 1952 (a)] respectively 5.5 per cent and 4.5 per cent, Fernandez [1953 (b)] 48.6 per cent, Basombrio et al. (1953) 58.3 per cent, Arguello Pitt et al. (1953) 92 per cent, Doull, Guinto & Mabalay (1957) 17.9 per cent (with standard error of 3.9 per cent), Olmos Castro et al. [1959 (b)] 81.2 per cent, Yanagisawa (1960) 86.9 per cent. Rosemberg, Souza Campos & Aun [1952 (a)] stressed the fact that "as found in earlier studies the conversion to positivity of Mitsuda reaction by BCG is rarely accompanied by a Fernandez type or early reaction (three instances in 66 Mitsuda reactions)". In a few groups of children studied, Bechelli (1961, 1964) reported that with BCG and lepromin re-testing there was a low proportion of positivity of early lepromin reaction or even an absence of same. The great difference in results could be attributed to the differences in samples studied and of lepromin; type, dose and

validity of BCG; reading criteria of early reaction, and interval between vaccination and lepromin testing.

It should be noted that Guinto, Mabalay & Doull (1962) arrived at a tentative conclusion that lepromin reactivity induced by a single BCG vaccination is lost to an appreciable extent within a few years.

In Beiguelman, Quagliato & Camargo's study (1965) a sample of 1251 contacts, not reacting macroscopically to lepromin, was retested with this antigen. 834 out of the 1251 contacts were vaccinated orally with BCG after the first lepromin test. The remaining 417 were not vaccinated and were used as controls. No difference was found between the groups in the proportion of macroscopically positive Mitsuda reactions revealed by the second test.

Beiguelman, Souza Campos & Pinto Jr. (1967) investigated the influence of BCG vaccination on the lepromin test in children born to parents, both lepromatous. They emphasized the ability of BCG vaccine in stimulating a macroscopically positive Mitsuda reaction even in those children considered to belong to a genetically susceptible fraction of the population. However, it was observed that the rate of strong Mitsuda positive reaction (++ and +++) after BCG vaccination among the offspring of lepromatous parents is significantly lower than that observed among the same age-group offspring of healthy parents contacts of leprosy cases.

The above studies provide evidence in favour of cross-sensitization. In some of these investigations the lepromin conversion in the BCG vaccinated people has not been significantly higher than that observed in the control groups. However, significant differences have been reported in some controlled studies and the results obtained in children 0-4 years old are most suggestive.

2. BCG and lepromin conversion in leprosy patients

Attempts to obtain lepromin conversion in leprosy patients have been chiefly limited to the lepromatous cases, because if BCG vaccination were able to determine an evident and persistent lepromin positivity in these cases, it would also be of benefit for healthy people. The proportion of lepromin conversion reported varied from 0 to 92 per cent: Convit et al. (1951), 40.7 per cent; Azulay, Moura & Mourao (1952), 35 per cent; Dharmendra, Mazumder & Mukerjee (1953), 5 per cent; Quagliato & Bechelli (1953), 4.5 per cent; Lowe & McNulty (1953), 11.5 per cent; Urquijo (1954), 44 per cent (intradermal BCG) and 46.2 per cent (oral BCG) ; Jonquieres and Masanti (1954) only doubtful and temporary reactions; Neyra Ramirez (1954), 86.6 per cent and Pereira (1956), 92 per cent! Costa & Teixeira (1953) and Contreras et al. (1958) did not observe lepromin conversion.

Schujman (1956) reported lepromin positivity in 47 per cent of lepromatous cases with oral BCG and in 50 per cent with intradermal BCG. However, this increased capacity of reactivity was only temporary: it started to decline after three months and disappeared five months after the BCG vaccination.

It should be emphasized that usually only weak positive reactions (1+) have been obtained and they seem to be temporary. Investigations undertaken with indeterminate cases are rare and without control groups.

3. BCG and lepromin conversion in laboratory animals

This study was undertaken in guinea-pigs, dogs, rabbits, rats, hamsters and Macacus Rhesus. Lepromin conversion has been reported by Chaussinand (1948), Olmos Castro (1954), Convit, Lapenta & Jorgensen (1955), Pereira & Guimaraes Filho (1955) and Azulay & Azulay (1958).

According to Hadler (1957), in the majority of the investigations in laboratory animals, only the clinical reading of the Mitsuda reaction was considered and, for this reason, they have no experimental basis. His studies (1953, 1956, and also with Ziti, 1955), based on the histological study of the lepromin reaction have shown:

(a) In animals which normally react in a positive way with lepromin (guinea-pigs), the previous inoculation of BCG modifies the reaction of the tissues to *Myco. leprae.* This is noted by an increase of the macroscopic and microscopic lesions, intensification of degenerative changes in cells and quicker lysis of bacilli; the constitution of the tuberculoid lesion is accelerated. These alterations are only quantitative and they do not mean lepromin

conversion. The type of histological reaction is not altered. The macroscopic reaction is larger after vaccination which has been improperly interpreted as an indication of conversion.

(b) In animals which normally give negative reactions to lepromin (rats), BCG also produces modification of the reactivity of the tissues when the suspension of *Myco. leprae* is injected. There is an increase in the macroscopic and microscopic lesions. However, the histological structure of the lesion does not present qualitative changes since, even after BCG, it continues to be formed by leprous cells with numerous bacilli. Consequently there is no lepromin conversion caused by BCG.

Shepard (1968) observed that "in a mouse that has been well vaccinated with BCG, or with oil-treated BCG cell walls, the immune response is triggered by a lower bacterial population and the plateau level is 10 to 100 fold lower".

C. Epidemiological studies and field epidemiological trials

*"According to the experience of many specialists and as stated by the WHO Expert Committee on Leprosy (1966) "Reactivity to lepromin increases rapidly with age, from negativity at infancy to almost universal positivity after adolescence in endemic areas and is associated with relative resistance". In the light of this and of the studies concerning the conversion of lepromin reaction in BCG-vaccinated subjects (summarized briefly above) we may make the following assumptions.

(i) It is doubtful whether BCG vaccination is useful to the small proportion of the population (perhaps about 5%—10%) either children or adults, unable to develop a positive lepromin reaction and therefore more prone to acquire leprosy and to develop the lepromatous type of leprosy. The limited, or doubtful, value of BCG vaccination in the prevention of leprosy was initially suggested by Bechelli, Paula Souza and their associates from studies in which it appeared that BCG had not increased significantly the proportion of lepromin reactors in certain groups of subjects, that in spite of vaccination there was always a certain proportion of non-lepromin reactors and that cross-sensitivity with tuberculosis infection would occur irregularly and within a limited range (Paula Souza, Ferraz & Bechelli, 1953; Paula Souza et al., 1953, 1956; Paula Souza & Bechelli, 1958; Bechelli et al., 1953. 1956; Bechelli, Quagliato & Nassif, 1953; Becelli & Quagliato, 1953, 1956; Bechelli 1957a, 1957b, 1958, 1962, 1966). Rotberg, (1953, 1957) drew attention to the doubtful value of BCG vaccination in anti-leprosy immunization on the basis of natural resistance to leprosy.

From the epidemiological point of view, this small population group (5%—10%) is the most important and the attention of leprologists is concentrated on it in order to prevent the appearance of the infectious forms of leprosy and to avoid the spread and maintenance of an endemic.

(ii) BCG vaccine might be useful to persons who, because of their age, have not yet been stimulated to develop a degree of resistance to *Myco. leprae.* as indicated by the lepromin test. Therefore, it could be of advantage mainly to children in the 0-4 years age-group and apparently would not be useful to the adult population, the great majority of whom are already lepromin reactors. In persons over 5 years of age, the value of the vaccination is likely to decrease as the age increases.

(iii) In those who have this potentiality, the development of resistance to leprosy following BCG vaccination might influence the incidence rate, and perhaps the form, of leprosy, its degree of severity and its progression."

The effect of BCG in the prevention of leprosy was or is being studied mainly in three controlled fields trials. Two of them are concerned only with child populations: child contacts in Uganda; child population, mainly that not exposed at home, in Burma. The study in New Guinea covers the entire population of an area of about 5,000 inhabitants.

The field epidemiological investigation should determine the immunizing power of the vaccine and the magnitude of protection. To measure the potential effect on the leprosy problem several parameters should be taken into account: incidence of leprosy in vaccinated children, classification of cases, degree of severity and evolution of the disease,

* From Bechelli et al., (1970). Reproduced with the authorization of the Bulletin of the World Health Organization.

proportion and degree of severity of disabilities, bacteriological status, lepromin reactivity, effect in contacts and non-contacts, prevention of lepromatous and borderline leprosy and, if possible, cost-benefit analysis of the vaccination in various epidemiological situations. Thus the epidemiological, clinical, bacteriological and economic impact should be studied against the background of the epidemiological, socio-economic and cultural situation in the area.

Since leprosy cases detected in the trial have to be treated, the natural course of the disease in vaccinated and unvaccinated children cannot be studied.

Such long-term epidemiological field studies are difficult to carry out and require an excellent team (team leader, statistician and laboratory technician) with a national counterpart (if the project is international), paramedical workers, clerks and drivers.

1. The trial in Uganda

"The trial began in September 1960, and the fourth and last round of follow up examinations was completed in September 1970. The participants were all child contact or relatives of known 'index case' of leprosy. All the children were examined on entry and given a Heaf tuberculin test. Those with leprosy on admission, or with strong positive reactions (Heaf Grade III or IV), were observed without vaccination; the others were allocated alternately to an unvaccinated group (8,065 children) and a BCG vaccinated group (8,085 children).

By the end of the fourth follow-up examination, 201 cases of leprosy (all non-lepromatous) had been diagnosed in the unvaccinated children, and 41 cases (including 1 lepromatous leprosy) in the BCG-vaccinated children. This represents a reduction in incidence of 80%, attributable (because of the random allocation and the 'blind' assessments) to the BCG vaccination.

The efficacy of BCG in this trial does not appear to be associated with the initial tuberculin reaction (i.e. negative, Grade I, or Grade II), the sex or age of the child, or the type of leprosy (lepromatous or non-lepromatous) in the index case. However, there appears to be a slight falling-off in efficacy in the third and fourth follow-up periods". (Stone & Browne, 1973).

2. The trial in Karimui

"This trial of BCG at Karimui began in 1962, and is continuing. The Karimui population is leprosy-endemic, tuberculosis free and situated in an isolated portion of the Eastern Highlands in the Territory of Papua-New Guinea. The total population (all ages) was randomly allocated to two groups—BCG vaccinated and saline receptors, and until 1967, remained untreated. The incidence of the disease was measured by serial surveys of the total population in 1964 and at annual intervals. Cases have been confirmed by biopsy; 87 cases occured in the vaccinated group and 148 cases in the unvaccinated.

Under the age of 5 years, vaccination does not confer protection, but between the ages of 5 and 24 years vaccination confers a significant degree of protection; after 25 years of age, no appreciable difference was noted in the incidence of the disease in the two groups. The results appear similar for males and females.

However, the protection conferred exhibits marked type specificity, as judged by histopathological criteria, with a highly significant degree of protection occurring in the BT group (Ridley's classification).

The pattern of age and type specific protection has remained constant throughout the trial. Tests of a sample of the population with standardized human and avian tuberculins indicate that (with the possible exception of males over the age of 25 years) infections with anonymous mycobacteria have not influenced the results, and it can be demonstrated that the vaccinated and unvaccinated groups are similar with respect to exposure to infection". (Russell, 1973).

3. The trial in Burma

In the controlled WHO trial in Burma the nine-year findings may be summarized as follows: "The leprosy incidence rates so far in the vaccinated and unvaccinated children aged 5-9 and 10-14 years [at intake] are similar. The BCG-vaccinated children aged 0-4 years at intake had an incidence rate [significantly] lower than that of children in the control group [protection rate of 38%]. BCG vaccination did not protect household contacts or children aged 5-14 years not exposed in the household, and did not influence the distribution of the forms of leprosy in the cases detected. The lepromin reaction in

relation to the age at intake was consistently stronger in the vaccinated children than in those of the control group; the younger the age group the more pronounced was the difference, which was only slight in the age group 10-14 years at intake. If the results of the late lepromin reaction are related to the age at onset (when the children are older than at intake), the differences between the BCG and the control groups tend to decrease. It does not seem that the BCG-vaccinated children suffer from a less serious form of leprosy than the nonvaccinated children (most of them nonreactors to tuberculin)". (Bechelli et al 1974).

—Taking into account the available reports, the Committee of Leprosy Control of the Tenth International Congress of Leprology (Bergen, 1973) decided the following:

"In view of the findings so far available from these trials, the committee considers it premature at this stage to recommend BCG vaccination or chemoprophylaxis as a regular part of the leprosy control measures. Further research is still needed in these important subjects" (1973).

The WHO Expert Committee on Leprosy (1977) stated that in the Burma trial "there has been no significant decline in the incidence of leprosy in the control group, the vaccinated group showed a protection rate of about 15%. Moreover it is noteworthy that 10 histologically confirmed multibacillary cases were diagnosed during 1974-75 in the Burma trial. Three were found in the vaccinated group (1 L, 1 BL, 1 BB) and 7 in the control group (2 BL, 1 BB, 3 L, 1 B). The fact that infectious forms have now appeared in the vaccinated group indicates the limited value of this measure. However, it is not clear whether any protection should be expected more than 5 years after vaccination.

It is considered that the position taken by the WHO Expert Committee in 1970 and restated at the International Leprosy Congress, Bergen, Norway, in 1973—that it is not yet possible to recommend BCG as a specific prophylactic measure for the prevention of leprosy—must be upheld. However, taking into account the protective values of BCG vaccination found in the Karimui trial in Papua New Guinea, the Mandalay area in Burma, and the Uganda trial, the Committee recommended that programme managers should ask the vaccination services to apply BCG vaccination to areas known to have high prevalence rates of tuberculoid leprosy. This would take advantage of the protective effect that BCG may have against tuberculoid forms of leprosy owing to its possible enhancement of resistance, whether specifically or nonspecifically. Vaccination cannot be regarded as an alternative to active case-finding. Those responsible for the planning and evaluation of control measures and who use BCG vaccination are requested to follow up detection rates carefully for periods of at least 10 years and to publish the results."

In our opinion, taking into account the incidence of tuberculoid leprosy in the BCG and control groups, their lepromin reactivity and evolution in the WHO trial (Bechelli et al., 1970, 1973 and 1974) it seems unlikely that BCG could affect substantially the pattern or trend of the disease, and the prevalence or the pattern of tuberculoid leprosy in the Burma trial area or in other areas with similar characteristics. The protective role of BCG has to be substantial to warrant its large-scale use for immunization against leprosy or against the tuberculoid forms of the disease.

SUMMARY

The findings so far obtained in the three trials to determine the preventive role of BCG vaccine against leprosy are strikingly different. It is hoped that further data from these trials, including those derived from the study of several parameters, may allow a definite conclusion on the protective role of BCG, its possible impact on the trend of the disease and its public health importance.

WHO Expert Committee on Leprosy (1977) consider that "the position taken by the WHO Expert Committee in 1970 and restated at the International Leprosy Congress, Bergen, Norway, in 1973—that it is not yet possible to recommend BCG as a specific prophylatic measure for the prevention of leprosy—must be upheld".

Progress in the microbiological studies on *Myco. leprae* should lead to the preparation of a specific vaccine. This would have a greater epidemiological impact if able to protect the small fraction of the population poorly prepared (genetically?) to deal with *Myco. leprae,* thus reducing the incidence of lepromatous and borderline leprosy. Perhaps even a specific vaccine may not be able to give this protection and/or prevent leprosy

in already infected individuals. An optimistic forecast of the vaccine potentiality should be avoided because of this and also of the relative resistance of most of the inhabitants in endemic areas, and of certain epidemiological aspects in regions of high and low endemicity. The magnitude of the immunizing power of the vaccine, its potential effect on the leprosy problem and its public health importance should be determined in long-term controlled trials in different epidemiological situations.

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CHEMOPROPHYLAXIS AGAINST LEPROSY

S. K. NOORDEEN

The need for a specific preventive against leprosy cannot be over-emphasised. The currently available method of control of mass treatment is essentially secondary prevention with its serious limitations. The ultimate solution to control and eradication of leprosy will in all probability be through a method of primary prevention. Chemoprophylaxis against leprosy can be one such method provided the drug used is highly effective, non-toxic, and easily applicable. Even if there are limitations to its effectiveness and easy applicability, chemoprophylaxis can still play its role in individual situations of high risk. Experience with regard to mass chemoprophylaxis in other diseases, however, is not very encouraging. With the exception of yaws, it has not been possible for mass chemoprophylaxis to make any serious impact in the control of communicable diseases. All the same it should be recognized that chemoprophylaxis has been successfully employed in individual situations in the control of diseases like malaria and tuberculosis.

The possibility of chemoprophylaxis against leprosy was thought of by several workers as a result of Dapsone being accepted as an effective chemotherapeutic drug. Since then number of trials on the value of Dapsone, and much later Acedapsone, as a chemoprophylactic have been undertaken. The studies have been carried out in Bombay, Chengalpattu, and Bobbili in India, and in South Korea, Philippines, Uganda, South Vietnam and Micronesia.

Figueredo[1] in Bombay was the first in India to try out Dapsone as a prophylactic. Based on a small sample of contacts he reported that Dapsone prophylaxis showed significant reduction in risk of infection. The study in S. Korea[2] was based on Dapsone prophylaxis of 325 children living in preventoria, with 435 similar children serving as control. Based on a follow-up of 2 to 7 years the incidence in the prophylaxis group was found to be only 0.6% as against 7.1% found among the controls. In another trial in the same country the incidence in a prophylactically treated group of contacts was found to be 1.7% as against 0.13% among controls. The studies indicate that Dapsone prophylaxis in Korea gave a very high protection of about 92%. The study in Philippines was carried out among 500 child contacts in a sanatorium divided into two equal groups, with one group on Dapsone and the other being kept as control. The protection for prophylaxis as estimated at the end of three years was about 44%. The study at Uganda[4] was carried out among school children in two adjacent areas. In one area school children were given Dapsone twice a week, while nothing was given to school children in the other area. The incidence among school children in the control area at the end of 3 years was 9.5 per 1000 whereas it was 1.2 per 1000 in the area where prophylaxis was given. The protection in this study works out to about 87%. The study in S. Vietnam[5] compared occurrence of leprosy among children of leprous patients kept in a hospital and receiving Dapsone prophylaxis with children of refugee patients coming to hospitals. It was found that whereas only 1 out of 91 children receiving prophylaxis developed leprosy, 47% of children among refugees were suffering from the disease.

The trial in Micronesia[6] used acedapsone, a long acting sulphone, as a chemoprophylactic. The entire population consisting of about 1400 living in three villages were given Acedapsone. The dose was 225 mgm. I.M. every 75 days for persons over 5 years of age, and 150 mgm. every 75 days for persons between 6 months and 5 years. The prophylaxis was combined with chemotherapy with Acedapsone for all leprosy patients. The prophylactic treatment was continued for about 3 years, and during this period except for 13% others took the treatment at least for sometime. A comparison made of occurrence of leprosy in the 3 villages during

the period prior to mass prophylaxis with the occurrence of leprosy during the actual period of prophylaxis, showed that as against 5.5 new cases normally expected during every half year no new case was detected during the period of prophylaxis except during the first 6 months of mass prophylaxis. Follow-up of the population after cessation of mass prophylaxis has indicated occurrence of a small number of new cases.

Chemoprophylaxis study at Bobbili

The study at Bobbili (Andhra Pradesh)[7] was carried out by Gandhi Memorial Leprosy Foundation in a population of about 40,000 with a prevalence rate for leprosy of over 3%, and living in 54 villages. The 54 villages were divided into 2 equal groups, prophylaxis and control. In the prophylaxis group of villages Dapsone was given twice a week to all healthy person upto 25 years of age; in the control group of villages all healthy persons below 25 years received a placebo. However the study could not be carried out by double-blind method, and allocation of villages to prophylaxis or placebo was not unknown. The coverage for administration of tablets was about 65%. The administration of the Dapsone in the 27 villages and placebo in the other 27 villages was continued for a period of 4½ years, and thereafter Dapsone prophylaxis was continued upto the 8th year only in half of the 27 villages which were under prophylaxis earlier. The follow-up was carried out through annual surveys.

The total number of new cases in the study in all the 54 villages during the first four years was 247. Of the 247, 55 (2 'L' and 53 'N') came from the prophylaxis group and 192 (9 'L' and 183 'N') came from the control group. The reduction in incidence of leprosy during the first four years in the prophylaxis group was of about 91%. The reduction in the incidence in the control group during the same period was about 42%. Therefore it was concluded that the net reduction in incidence attributable to chemoprophylaxis was of the order of about 49%.

Table-I shows the occurrence of leprosy in the two groups of villages.

TABLE I

	Prophylaxis villages	Control villages	Reduction in incidence (%)
Incidence per 1000:			
1st year	2.53	4.79	47%
2nd year	1.17	5.36	78%
3rd year	0.74	3.01	75%
4th year	0.24	2.78	91%
Reduction in incidence in 4 years	91%	42%	

The study was continued in a modified form[8] from the fifth to the eighth year when half of the villages which received prophylaxis earlier the drug was discontinned and in the other half it was continued. The difference in the incidence rates between prophylaxis and control villages was continued to be observed but to a lesser extent. During the eighth year (1971-72) the incidence in the villages which received prophylaxis throughout the eight years was 0.43 per 1000, in the villages which received prophylaxis during the first four years and later discontinued it was 1.46 per 1000, and in the control villages which received placebo throughout the eight years the incidence was 1.31 per 1000. Table-II shows the incidence in the three groups from the fifth year onwards.

TABLE II

	Villages where prophylaxis was continued without interruption	Villages where prophylaxis was given for 4 years and discontinued thereafter	Villages under control with placebo for the first 4 years and nothing thereafter	Reduction in incidence under prophylaxis %
Incidence in the 5th year	0.46	0.62	1.87	75%
,, 6th ,,	0.60	1.04	1.28	53%
,, 7th ,,	0.30	0.15	0.98	69%
,, 8th ,,	0.43	1.46	1.31	67%
Reduction in incidence in 8 years	91%		73%	

From the table it appears that cessation of prophylaxis in certain villages has leod to increase in incidence after such cessation. Moreover the protection attributable to chemoprophylaxis itself which was about 49% at the end of 4 years had come down to 18% at the end of 8 years. Instead of working out rate of protection through comparative reduction in incidence over a period, if the comparisons are made on concurrent incidence rates in the two groups for the 8 different surveys the protection appears to be high and fairly consistent with an average protection of about 69% and with a range of 47% to 91% for the different years.

The study was continued from 9th year without giving any prophylaxis to any group, but continuing with the annual surveys of all the 54 villages. Upto the 11th year the incidence rate in the group of villages which was originally under prophylaxis has tended to show an upward trend; however incidence rate in this group was still less than what was observed in the original control group of villages.

There are certain interesting observations in the study which are difficult to explain, the first of which is the reduction in leprosy in the control group itself which is attributed to the usual mass treatment of patients. Incidence of leprosy came down in the control group by 42% in 4 years and by 73% in eight years. Even in the population over 25 years who were not participating in the prophylaxis leprosy incidence came down by 62% in 4 years and by 75% in 8 years. Such marked reductions in incidence in short periods is rather unusual.

The Bobbili study indicates that even under a moderate coverage of 65%, prophylaxis with Dapsone could be effective for populations below 25 years of age.

Studies on chemoprophylaxis at Chengalpattu

The first study was carried out between 1961 and 1967 in a part of Chengalpattu District of Tamilnadu having a population of over 200,000. The objective of the study was to find out the value of chemoprophylaxis with Dapsone among household child contacts of lepromatous and other bacterio-positive cases of leprosy.

The study was well controlled with half the contacts receiving Dapsone tablets and the other comparable half receiving identically looking placebo tablets. The number of contacts studied was about 700. The study was completely double-blind. The tablets were administered twice a week in person by specially trained field workers under intensive supervision. The children received the tablets as long as the source of infection was active and for a further period of three years. The dose of Dapsone administered was 75 mgms. twice a week for children in the age group 11 to 15 years, 50 mgms. twice a week for those in the age group 6 to 10 years, 25 mgms. twice a week for those in the age group 3 to 5 years, and 10 mgms. twice a week for children below 3 years. New cases among the contacts receiving either Dapsone or placebo were detected by periodic examinations by physicians once in three months. The study lasted 5½ years.

The study produced in all 71 cases of leprosy, 48 cases in the Control group receiving placebo tablets, and 23 cases in the Prophylaxis group receiving Dapsone tablets. Allowing for the different periods of follow-up for different contacts and calculating incidence per unit of 100,000 person-weeks of treatment, it was found that the incidence of leprosy among the contacts in the Control group was 74.3 per 100,000 person-weeks and that in the Dapsone group the incidence was 35.3 per 100,000 person-weeks. The difference was statistically highly significant. The incidence showed that the protection given by chemoprophylaxis against leprosy was about 52.5%. The degree of protection was quite considerable. The study showed that the efficacy of chemoprophylaxis was not uniform and that certain sub-groups among the contacts received greater protection than others. However, one factor that was common to all the sub-groups which received high degrees of protection from chemoprophylaxis was their comparatively high risks of acquiring leprosy. No toxic side effects were noticed among the children receiving the tablets during the 5½ years of study.

Regarding the duration of prophylactic treatment in the study, a further 8½ year follow-up of certain contacts showed some interesting results[10]. The 8½ year follow-up was carried out among contacts of lepromatous cases who had treatment with either Dapsone or placebo earlier, and whose 'treatment' had been terminated following their index cases having been declared inactive. The declaration of inactive state was

based on bacteriological negative state maintained for at least three years as verified through six half yearly skin smear examinations. The follow-up showed that contacts who originally were taking Dapsone continued to receive protection even after stoppage of treatment whereas contacts who did not have Dapsone originally continued to run higher risks of getting leprosy as compared with their counterpart. The incidence in the original prophylaxis group was 13.9 per 100,000 person-weeks, whereas in the control group it was 31.6 per 100,000 person-weeks, showing a protection of 56.1%. It is difficult to explain this 'carry over' benefit from chemoprophylaxis, unless it is hypothesised that contacts studied consisted mostly of infected persons without manifest disease and chemoprophylaxis eliminated all the organisms from the system of those persons.

To clarify some points arising out of the first study, such as effectiveness of altered more practicable dose schedules, effectiveness among contacts of Non-lepromatous types of leprosy, and effectiveness under conditions where duration of treatment could be less than 3 years, further extended studies were carried out in a new area[11].

The studies were carried out in a different part of Chengalpattu District with a population of over 210,000. The duration of the extended studies was six years. In this population 955 contacts of lepromatous cases, and 2000 contacts of non-lepromatous cases, all free from any evidence of leprosy were identified for inclusion.

The 955 lepromatous contacts were divided into three equal groups of 318, 318, and 319 after stratifying by age and sex. The actual division was based on random allocation within each age-sex group. The three groups were designated as Group A, Group B, and Group C. Group A consisted of those who received Dapsone once a week at the rate of 75 mgm., 50 mgm., 25 mgm., and 10 mgm., respectively for age groups 11 plus, 6 to 10, 3 to 5, and 1 to 2. Group B consisted of those who received Dapsone once a week at the rate of 50 mgm., 25 mgm., 10 mgm., and 5 mgm. respectively for the same age groups. Group C, the Control group, consisted of those who received placebo tablets of Dicalcium Phosphate once a week. Thus, the study was expected to evaluate the effectiveness of Dapsone as a prophylactic in once a week dose schedule and in two different doses.

The 2000 non-lepromatous contacts were divided, by using random allocation, into two equal groups of 1000 each after stratification by age ands ex. One group consisted of those who received Dapsone twice a week at the rate of 75 mgm., 50 mgm., 25 mgm., and 10 mgm. respectively for age groups 11 plus, 6 to 10, 3 to 5, and 1 to 2. The second group, which was the control group, consisted of those who received placebo tablets. The studies were conducted using double blind procedures.

The administration of the tablets was quite intensive and contacts received about 90% of the expected treatment. Administration of tablets was continued for the contacts for the period the index cases were active and for 1 to 2 years thereafter.

The follow-up examinations of contacts, to detect new cases of leprosy, were carried out by a field medical officer once in three months for lepromatous contacts and once in six months for non-lepromatous contacts.

By the end of 6 years, the total number of new leprosy cases that occurred in the study on contacts of lepromatous cases was 91, of which 38 were from the control group, 26 from the prophylaxis group A, and 27 from prophylaxis group B.

The 38 cases in the control group had occurred among contacts whose total participation in the study was 35,435 person-weeks; the 26 cases in the prophylaxis group A had occurred among contacts whose total participation in the study was 40,193 person-weeks; the 27 cases in the prophylaxis group B occurred among contacts whose total participation was 40,177 person-weeks. The incidence rate in the control group was 107.2 per 100,000 person-weeks, whereas the incidence in prophylaxis group A was 64.9 per 100,000 person-weeks, and in prophylaxis group B it was 67.2 per 100,000 person-weeks. The difference in the incidence of leprosy between the control and prophylaxis group A in this study was statistically significant ($t = 1.98$; $p < 0.05$); the difference between control and prophylaxis group B was not statistically significant ($t = 1.85$). Prophylaxis with Dapsone in the study had given a protection varying from 39.7% in prophylaxis group A to 37.3% in

prophylaxis group B. There was no case of lepromatous leprosy among either the 26 cases in Prophylaxis group A, or the 27 cases in the Prophylaxis group B, or the 38 cases in the Control group.

The total number of new leprosy cases that occurred in the study on contacts of Non-lepromatous cases was 181, of which 109 were from the control group, and 72 from the prophylaxis group. The 109 cases in the control group had occurred among contacts whose total participation in the study was 136,631 person-weeks; the 79 cases in the prophylaxis group had occurred among contacts whose total participation in the study was 138,062 person-weeks. The incidence rate in the control group was 79.8 per 100,000 person-weeks, whereas the incidence in prophylaxis group was 52.2 per 100,000 person-weeks. The difference in the incidence of leprosy between the control and prophylaxis groups in the study was statistically highly significant ($t = 2.82$; $p < 0.01$), and showed that among contacts of Non-lepromatous leprosy prophylaxis with Dapsone gave a protection of 34.6%. There was no case of lepromatous leprosy among either the 72 cases in the prophylaxis group, or the 109 cases in the control group.

Based on further analyses of data the following additional conclusions could be drawn from the extended studies.

(i) Protection given by prophylaxis in either study was more or less limited to children upto 12 years of age. The older children received little protection.

(ii) Among contacts of lepromatous cases, the protection through chemoprophylaxis with Dapsone appeared to be significantly influenced by certain geographic factors. Protection through prophylaxis appeared to be very high in areas where contacts were running very high risks, possibly due to factors such as high density of population and high leprosy prevalence in those areas.

(iii) Follow-up of contacts after termination of treatment had indicated that there may be a 'carry over' protective effect for contacts who were under prophylaxis earlier.

From all the studies on chemoprophylaxis, it can be concluded that chemoprophylaxis with sulphones is moderately effective when administered intensively. The dose of Dapsone can be as low as 1 to 2 mgm. per Kg. body weight per week, and could be administered as once a week dose. So far it is not possible to state whether chemoprophylaxis could prevent occurrence of lepromatous leprosy, as very few lepromatous cases have been observed even in the control groups of the studies. In order to find an answer to this it may be necessary to have larger number of subjects under study and for longer periods. There also appears to be a 'carry over' benefit for chemoprophylaxis as observed in some studies. So far in none of the studies have any serious side effects due to sulphones been met with.

Although we have an answer with regard to effectiveness of chemoprophylaxis in various groups, it cannot be said of the same with regard to the feasibility of mass chemoprophylaxis as a method of control[12]. No operational studies have been undertaken so far to answer this question. But from all available evidence and indications it can be reasonably stated that mass chemoprophylaxis of even a high risk group such as household contacts is not going to be easy. Further the impact on the incidence of leprosy in the community by protecting to some extent only the household contacts will only be marginal. Contacts of all types, although admittedly running much higher risk of getting leprosy, contribute to less than one fourth of all new cases. The bulk of the new cases in endemic areas occur among persons who do not have any case of leprosy in their households. Although they run a comparatively very low risk their numbers are so large as to contribute to the bulk of the incidence. The other problem with Dapsone prophylaxis is the need to administer the drug over a long period. In the light of the difficulties encountered in keeping leprosy patients under regular treatment over long periods, the difficulties in treating healthy subjects over long periods cannot be overemphasised. The feasibility of chemoprophylaxis against leprosy may improve if the initial hopes of Acedapsone as a chemoprophylactic are confirmed (The Central Leprosy Institute is already undertaking a study on Acedapsone prophylaxis). Notwithstanding the difficulties that are likely to be encountered if Dapsone is used in mass chemoprophylaxis, the drug can still be recommended for chemoprophylaxis in individual situations, where the risk of getting leprosy is unduly high and where there is sufficient motivation for prophylaxis.

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LEPROSY CONTROL IN URBAN AREAS-OUTLINE OF AN APPROACH

D. S. CHAUDHURY

Leprosy in urban areas of developing countries is a growing public health problem. This calls for serious attention and concerted actions. In India with 3 million leprosy patients, 30% of the problem is located in urban areas which accomodate 20% of the total population of the Country.

For socio-economic reasons, urban leprosy control is a more complicated task compared to the programme in rural areas. The general outline of an approach to the subject is given in this paper but the details of methods will vary in relation to the size, composition and growth pattern of different urban areas.

Rapid and phenomenal growth of urban areas has led to exodus of rural population into the cities with resultant population explosion. Effective urban leprosy control work should be related to good coverage of the surrounding rural areas.

Untramelled urbanization creates many social and health problems. Slums and shanty towns proliferate which are grossly ill-planned. Living conditions in such slums are often worse than that of the most depressed rural areas. This urban squalor is more acute in some of the Metropolitan Cities where growth of industries have caused influx of population from a wider catchment area. There is greater mobility of the population in this situation. All these can create conditions favourable to the spread of leprosy if the number of infectious cases living in the area is sufficiently high.

Control of leprosy in such situations should be closely linked with other measures related to urban planning and promotion of health. This vital link has to be recognised. Overcrowding in poor houses, environmental distress, lack of health awareness and absence of basic health care facilities are important factors contributing to the endemicity of leprosy. Specific medical measures of case finding, treatment and health education should be further reinforced with measures of slum clearance, better housing and water supply, nutrition aids and guidances, basic health care and family welfare schemes. Creation of urban health centres and health posts in slum areas where disease control activities can be judiciously integrated with follow up, close surveillance and health work will meet the large community needs and will foster more productive community participation.

The prejudice against leprosy is still enormous. There is exaggerated fear of aversion to this problem even in informed minds. A limited drug based approach can not solve such a vast social problem with deep psychological inhibitions unless it is coupled with other parallel and promotive health and educational ventures. Only then, control of begging, rehabilitation of the handicappeds and reintegration of cured leprosy patients will be possible. The problem calls for restructuring of health service infrastructure and community-oriented training of health workers who should be mentally prepared to align themselves with teachers, social workers and community leaders to achieve control of disease through an integration of medical, social and educational efforts. Closest cooperation should exist between health workers and Municipal Organizations.

In Metropolitan cities, Co-ordinating Committees with representations from the Government, Municipal Organization, Social Wel-

fare Board, Voluntary Organizations in leprosy, Various Service Clubs and Welfare Organizations should be formed to develop a master plan for the Metropolitan area, identify areas of cooperation, define priorities and programmes and coordinate technical supports.

The clear definition of the objectives of leprosy control must be underlined in all planning so that inadequate attempt or mere sentimental approach do not vitiate ultimate public health priorities.

Tracing of leprosy cases in examination of contacts, school children and slum dwellers, treating all leprosy patients in convenient places in the community and teaching the patients and the Public about health care remian as the essentials in leprosy control.

URBAN LEPROSY PROBLEM AND IT'S CONTROL-PROFILE OF A PROJECT

WILLIAM GERSHON

The advent of 20th Century brought in its wake revolutions in urbanization and industrialisation all over the world. Along side the various advantages that accrued to the mankind, it also helped in the proliferation of slums.

At the beginning of 19th Century, only 2% of the World's population lived in the cities. By the year 2000, the world population is estimated to be 6500 million of which, about 50% will live in urban areas.

The process of urbanization is taking place at a much greater pace in the developing countries, where communicable diseases pose a big problem. In the past 50 years, urban population in South Asia has increased by nearly 14%, as compared to the global average of 80%. In absolute terms the number of people living in ruban areas in India has increased to over 110 million in the last 50 years. The increase in the population of cities is mostly attributable to the city-ward influx of the rural population, as cities attract the rural poor because of various job opportunities. However, rapid population growth in urban areas continues to outpace the capacity to provide even the very basic and minimum services to all. A rural to urban migration exacerbates the situation, creating an overwhelming demand for the urban services worst reflected in the numerous slums.

The slum as defined by Oxford Dictionery is "A street, alley, court etc. situated in a crowded district, town or city and inhabitated by people of low income classes, or by very poor—many such streets or courts, forming a thickly populated neighbourhood of squalid and wretched character." Further the Government of India Slum Areas (Improvement) Act, 1954, defines slum as any predominently "residential area, where the dwellings by reason of dilapidation, over crowding, faulty arrangement, lack of ventilation, light or sanitary facilities or any combination of these factors, detrimental to safety, health or morals".

Mostly and generally the people in the slums have to lead a life which is worse than rural life, because of their low-income, under-nutrition, inadequate housing and poor environment. This has given rise to numerous health problems. Like all communicable diseases leprosy also thrive in Slums.

It is an experience and a fact that the poor in the cities are the same people as the poor in the villages with the same socio-economic background. In short a slum is an overgrown village with similar patterns of social interaction and group response.

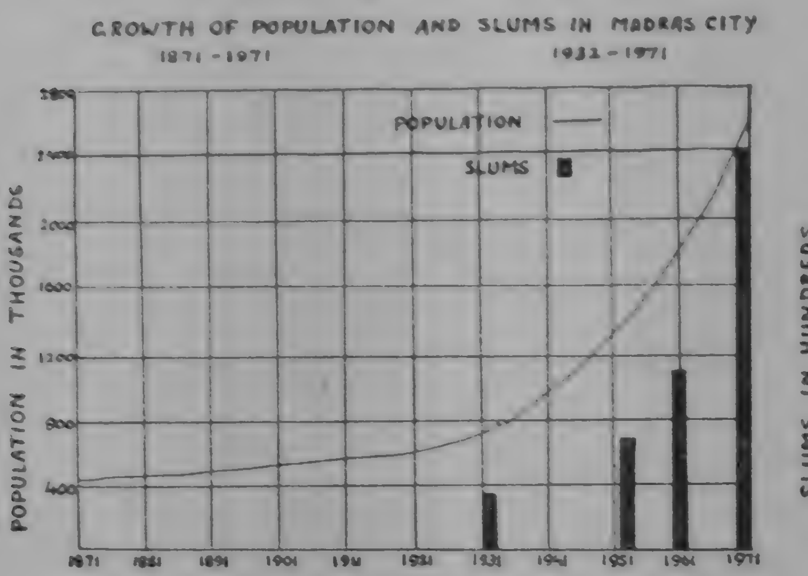
Mr. Jai Sen in the "Unintended City" says, "the argument that is being followed is that the development is impossible by definition if dependence is allowed to exist or worse still encouraged; and that aid can too easily be an encourager. Development can only occur through the growth of self reliance. And at present it secures that all the forces are working against the poor in cities from achieving this position of self respect".

SLUMS OF MADRAS

Madras too is a city which has a colossal problem of slums. As per 1971 census, it has more than 1200 slums inhabited by 8,00,000 persons, i.e. every third person of 2.5 millions in Madras lives in slums. The number of slums that was 181 in the year

1932 rose to 548 in 1961 and 1202 in 1971 (Fig. 1).

Fig. 1



A typical slum hut is made of mud walls and roof of miscellaneous articles. It consists of generally one all purpose room. The hut is vulnerable to fire and can easily crumble and collapse in rainy season. The living space available to a slum dweller is far below the minimum norm for a healthy living. The density of population in slums is nearly 1,00,000 persons per sq. km. compared to 20,000 persons for the non-slum areas.

A slum dweller already tormented by his proverty and surrounded by unhygienic environment falls easy prey to infectious and communicable diseases—leprosy being one of them. Realising the magnitude of the problem of leprosy in Madras, the German Leprosy Relief Association started in April 1971 a Pilot Project in Madras called Greater Madras Leprosy Treatment and Health Education Scheme.

AIMS AND OBJECTIVES

The objective of the scheme is to control leprosy in Greater Madras in an efficient and economic way and to evolve and standardize a pattern of urban leprosy control.

AREA OF OPERATION & POPULATION COVERAGE

To begin with, North Madras with a population of about 16 lakhs, was chosen as the Project area. This area is predominently industrial and hence congested. For operational convenience, this population of 16 lakhs has been divided in 3 distinct groups:

1. Slum Population—5 lakhs or 30% of the total population.
2. School going children—4 lakhs or 25% of the total population.
3. Other population—7 lakhs or 45% of the total population.

METHODOLOGY

Basically the methodology adopted by us compares with guiding principles of S.E.T. set down in the operational guidelines of National Leprosy Control Programme. But considering the special features of the urban population and its infinite complexes, we have modified our approach. We have therefore decided to cover the 3 distinct population groups mentioned earlier by a 3 tier programme of case finding i.e.:

1. Slum population to be covered by intensive house to house examination
2. Systematic physical examination of all the school going children.
3. Extensive health education of the population with particular emphasis on the remaining population.

ORGANISATIONAL SET UP—FIELD UNITS

The area of operation has been divided into 5 convenient zones. Zones are further subdivided into control units, managed by two para medical workers. Wherever local circumstances make it necessary, the size of the control unit has been adjusted to the local conditions depending on leprosy prevalence and population density. The para medical worker living in the area is responsible for the case finding among the population of the area, follow up, and further management of the detected cases.

CLINICS: OUT PATIENT TREATMENT CENTRES

15 Peripheral clinics are located at strategic places, keeping in mind the facilities available for the patients, so that they can attend the clinic without much inconvenience. The clinics are conducted in the places provided by Corporation of Madras, Slum Clearance Board, and other voluntary social welfare agencies. These clinics are held once a week on a particular day. The clinics are attended

by a team consisting of a doctor, physiotherapy technician, lab. technician, the local para medical workers, cobbler and a dresser.

In addition to the above clinics, a clinic is conducted at Headquarters mostly from the benefit of the patients from outside the project area. A general skin clinic is also conducted once in a week at Headquarters. This clinic is equipped with facilities for physiotherapy and minor surgery.

We also conduct 3 clinics in South Madras on behalf of the New Residents Welfare Trust, an agency involved in the social welfare of the resettled slum dwellers and, Guild of Services.

HEADQUARTERS

The technical and normative systems are planned, supervised and evaluated, and periodical meetings of the Senior staff are held at Headquarters. The offices of the Director, Field Staff and administrative staff are also located here. In addition, laboratory, physiotherapy unit and shoe departments are located at the Headquarters building.

STATISTICS

Procedures in the project are standardized. Recording and reporting are limited to what is essential for supervision, periodical evaluation and assessment. The basis of the statistics is the individual treatment card supported and complemented by contact survey cards, school survey forms, mass survey forms and bacteriological report forms. Workers finalise their individual reports and present them to the senior workers in the headquaters every month. The senior workers consolidate the report for the project.

PHYSIOTHERAPY UNIT

A physiotherapy technician visits the clinics at regular intervals and assesses the disabilities and deformities of the patients. The patients are educated in general about the care of anaesthetic hands and feet. Patients needing special care are educated individually. The visit of the technician is also utilized to teach the Para Medical Workers about the basic principles of physiotherapy, so that they can carry on the educational programme on other days. Patients who need special physiotherapy are referred to Dayasadan, the in-patient section of the project. P.O.P. (Plaster of Paris) Casts for non-infected dry ulcers are given in Dayasadan. Patients needing surgical intervention are referred to Vellore.

LABORATORY

Laboratory technician visits the peripheral clinics and takes smears from all infectious cases and also cases with doubtful classification, for diagnostic purposes. Smears taken in the field are brought to laboratory for bacteriological examination and the results are recorded in a book and in bacteriological report form, which once again is transcribed by the Zonal worker in the treatment card. Smears are taken twice a year for infectious cases.

SHOE DEPARTMENT

So far 565 micro cellular rubber foot wear were supplied to the patients. 1946 minor repairs were attended to in the clinics.

The following few pages deal with the actual pattern of work, and the results obtained through it.

CASE FINDINGS

Case finding activities mainly revolve around the 3 pronged action programme as described earlier. i.e., Slum Survey, School Survey and Health Education.

A. SLUM SURVEY

Slum population is covered by house to house examination. Before starting the slum examination, the survey team and the para medical worker in-charge of the area pay several visits to the slums. They were given a general picture of leprosy problem in India, with particular emphasis on Tamilnadu and the city of Madras.

Small committees consisting of slum leaders were formed. These committees were and are still active. In consultation with these committees a date is fixed for film and slide shows and a brief talk on leprosy. Thus the population is made aware of the general facts about leprosy. On the day of Survey, each block or street leader volunteers to stay back and accompany the survey team. Their approaches ensure total community participation and commitment.

First phase of slum survey was completed in December 1974. Here it is worthwhile to mention that the mass examination in

Urban area is a task that demands a lot of tact and 'diplomacy' from the Para Medical Workers.

Out of the 3,04, 227 population enumerated, 2,48,348 persons were examined which is 82%. 3,349 cases were detected with a leprosy prevalence rate of 13.6 per thousand (Table 1).

POPULATION CHANGE & FREQUENCY OF SURVEYS

We did a sample re-survey in one of the old control unit areas. Out of the old enumerated population of 10,954 persons 870 (7.8%) had left the slum. On the other hand 7,721 (43%) persons had immigrated in to these slums. This immigration rate is rather high.

Among the old population 5,520 were examined in resurvey and 21 cases were detected—a prevalence rate of 3.8 per thousand. Only one person was suffering from lepromatous form of the disease. Incidentally this person was not examined during the first survey. Out of the immigrant population, 3,846 persons were examined and 50 cases were detected—a prevalence rate of 13 per thousand. All of them were suffering from non-lepromatous form of the disease (Table 1A).

It is therefore evident that there is considerable rate of movement of population and hence it is advisable that resurveys should be carried out once in three years. If that is not possible, it should be done at least once in five years. In the meanwhile all other activities of case finding should go on normally.

B. SCHOOL SURVEY

A sizable number of total detected cases have been uncovered by school surveys. The advantages of school survey are:

(1) School going children form a significant part of the population and they are generally easily accessible and take much less time for screening.

(2) School children form a fairly representative sample of the various social, economic and ethnic communities in an area.

(3) Cases detected among school children help tracing other secondary cases in the family or neighbourhood.

(4) As a disease and vis-a-vis its treatment, the cases found in schools are generally in early stages and eminently responsive to treatment. These cases are thus prevented from developing deformity and progressive form of the disease.

ORGANIZATION AND PROCEDURAL APPROACH

Before commencing school survey, we had to contend with certain administrative problems like acceptance of our survey team by the school authorities. The Educational Officer of the Corporation of Madras and District Educational Officers were approached to issue a circular to all the schools under their respective control to accord permission to our survey team to examine the children. Secondly systematic health education of the teachers and the senior students was taken up. It was made a rule that the visit of the survey team to a school should be preceded by a lecture on leprosy.

During the first survey, out of the total 2,20,245 students on roll, 1,87,325 (85%) were examined and 2,013 cases (11 per thousand) were detected. Only 6 of the total detected cases were suffering from lepromatous form of the disease (Table 2).

RE-SURVEY OF THE SCHOOLS

We started the second survey in January 1975. We were particularly careful to maintain uniform time interval of about 2 years between the first and second survey. By the end of 1976, we could complete the second school survey, in which 2,10,455 students were enumerated and 1,77,583 students were examined (84%), 1,402 cases were detected (7.9 per thousand). It is very interesting to note that none of the child patient was suffering from lepromatous leprosy.

C. SURVELLANCE OF HEALTHY CONTACTS

All the healthy contacts of registered patients are recorded in contact survey cards and kept under surveillance. Maximum efforts are made to visit the patients' families for examination of the contacts within 3 months of their registration. The contacts are examined once a year. As on December 1976, there were 28,281 contacts under observation of whom 665 established cases of leprosy were detected (23.5 per thousand) (Table 3).

HEALTH EDUCATION

It is essential to start a leprosy campaign with health education and it must be continuously and patiently emphasised during the development and progress of the control activities. The aim of the health education is to arouse a rational attitude towards leprosy in the various population groups and the patients and their families.

Health education is given to the two following groups separately, namely:

1. The patient and his family
2. The general public

Each and every patient shcould be educated to convince them of the necessity to take regular treatment which may run for several years, and also give them and their families elementary knowledge about leprosy, its cause, mode of spread & curability.

The aim of educating the general public is to create awareness of early symptoms, treatment, control measures and the social responsibility of eliminating the disease. The most important thing is to involve the population, with whom and for whom we are working. The partnership is best promoted by practical demonstration of our activities.

Special emphasis is laid on the involvement of (1) Medical Practitioners (2) Teachers (3) Selected Groups—Lawyers, Service clubs, Nurses, Social Workers etc. (4) Voluntary Organisations.

Orientation courses for 200 medical practitioners were conducted. Post-graduate students of local medical colleges were also given lectures on leprosy. As a result of which the local medical practitioners are referring the cases to us for consultation.

Teachers, who are considered as agents of change play very important role in bringing about a change in social attitudes. So far 2000 teachers have been given lectures on leprosy, with demonstration of slides. A class on leprosy to the teacher trainees has formed a part of their regular training.

A study regarding the prevalent notions among the teaching community was conducted. A questionnaire, was circulated among 1000 teachers. The responses were interesting and are highlighted below:

Is Leprosy Curable? 87.3% persons are emphatic that leprosy is not curable. 10.7% of the respondents believe leprosy is curable. 2% have no answers.

Cause of leprosy : 23.5% believe that it is a hereditary disease. 40.2% believe that leprosy is venereal in origin. 17.9% believe that leprosy is caused by uncleanliness; 4.3% says leprosy is due to vitmain deficiency. The rest are undecided.

Is your fear of leprosy due to (a) Contagiousness (b) Deformity and Disfiguration

48.6% say their fear of leprosy is due to its contagiousness—48.7% are convinced that their fear is due to disfiguration and deformities.

Can a cured leprosy patient be allowed to mix with society freely

6.8% replied in the affirmative. 31.2% replied in the negative. 6.2% were conditional in their answers.

Would you purchase things sold by leprosy patients?

92.3% replied in the negative.

It is evident that among the teachers there is a great deal of misconceptions about leprosy. Our health education is therefore directed to remove such notions from teaching community.

To find out how far health education programme has brought about a change in the attitude of the teachers, a post-lecture evaluation has been undertaken.

Lectures on leprosy have been incorporated in the syllabi of the 3 social work teaching institutions.

Apart from this, the Madras School of Social Work and Nava Nirmana Social Institute assign final year students for field training with us. Some of the students from Madras School of Social Work and Layola College have submitted dessertations to the University of Madras, few of which are listed below:

(1) People's attitude towards leprosy;

(2) Socio-economic study of leprosy patients in a self settled leprosy colony;

(3) Conjugal life of leprosy patients;

(4) Attitude of leprosy patients towards the disease;

(5) Evaluation of the domiciliary rehabilitation programme.

In addition, a score of other papers on leprosy and allied problems were published in various journals by the students.

Voluntary organisations such as mothers' group, youth groups, adult literacy groups, social service agencies are being persistently kept involved in the programme.

Conventional methods of visual aids like film and slide shows, flannel graphs, flip charts and exhibition of slides in theatres, are being made effective use of. Exhibitions are also conducted. The slides in theatres have been exempted from tax and are being shown free as matters of public importance. A television documentary on methodology of urban leprosy control was telecast on 26th January. During leprosy week celebrations, a talk on Madras All India Radio was broadcast.

The impact of our many faceted and intensive health education programme can be realised when one knows that till December 1976, 4,854 cases have reported voluntarily to our various peripheral clinics.

Table 4 gives a comparative picture of case detection methods.

CASE HOLDING

This means ensuring that cases detected in surveys take regular treatment unitil he or she is certified cured or disease-arrested. This is of paramount importance in leprosy control. Irregularity is generally due to ignorance, disinterest or disability of the patient. It can also be attributed in part to indifference and casualness of the control program personnel.

A patient should be told the absolute necessity of regular treatment on the very first day of his registration. Invariably, the initial talk is very often ineffective, patients become irregular, and the failure to maintain a high case holding rate is a serious drawback of the control programme.

Education of all concerned is the best method to solve this. We therefore carry on an unceasing campaign of educating the patients about the absolute necessity of regular treatment. We endeavour to find out the causes of absenteeism and analyse them. We strongly feel that the treatment program should take into account various problems which deter a patient from attending regularly.

IN-PATIENT TREATMENT FACILITIES

After launching the project in the city and as the number of patients started increasing, we faced the problem of hospitalising patients who require specialised intensive care. Dayasadan, the beggar home run by the North Indian Business community came to our rescue. Dayasadan is situated in the centre of the city and the authorities placed at our disposal a ward with ten beds for hospitalising patients from the project area. With the permission of the management of Dayasadan, we have added one more ward with ten beds, making a total of twenty beds to serve the project area. Patients suffering from reactional episodes, eye complications, early primary deformities, ulcers and intercurrent diseases are temporarily hospitalised. On the subsidence of acute phase, the patients are discharged and advised to continue treatment from their respective peripheral clinics (Table 5 and 5A).

Based on the experiences gained in Madras we started three similar projects in Visakhapatnam, Calcutta and Bombay. Population covered by Visakhapatnam, Calcutta and Bombay projects are 5 lakhs, one lakh sixty thousand and 6 lakhs respectively. Brief information about Visakhapatnam and Calcutta is contained in Table 6. The programme in Bombay has been started only very recently.

CONCLUSIONS

The peculiarity of Urban leprosy campaign is the high rate of drop out cases. This is directly in proportion to the transmigration of the general population particularly in slums. The composition of the slum population in the metropolitan cities has regional variations. While in Madras 85% are from within the state of Tamil Nadu, in Calcutta and Bombay, majority of the slum dwellers are from outside the states. Secondly it is also attributable in part to frequent changes in the residences within the project are a itself.

It is advisable that in metropolitan cities where there are Medical colleges, teaching hospitals, corporation and ESI hospitals and various welfare agencies, a Central registry

of cases being treated by them be maintained. For this a well knit co-ordination committee should be formed and information regarding patients should be transmitted to the agencies. This will avoid duplication and enhance effectiveness of the control programmes.

It is our experience that patients have to face untold miseries when referred to general hospitals for investigations and treatment of complications other than leprosy. In endemic areas where it is necessary to have a special services project, it should be possible to enlist the co-operation of the general hospitals to render specialised consultancy services for the general complications of leprosy patients. In the long run it will help the integration at the base.

School surveys definitely and positively plays very important role in urban leprosy control. It not only helps in discovering early cases, but also provides momentum to health education programme as a whole. Health education activities are useful only when they are supported by active case detection and treatment work. Care is taken to underline the fact that leprosy control does not consist only in dishing out treatment to leprosy patients in any area. In fact this is a comprehensive community health work which aims at certain definite results beneficial not only to the patients or their families but to the community as a whole. For that reason maximum involvement of the community should be aimed at. Leprosy control activities must be implemented in the most practical and economical method justifying the cost-effectiveness analysis.

Systematic follow up of the patients treated should be undertaken at periodical intervals and patients inactive should be promptly released from control after they have completed the recommended period of maintenance treatment. Last but not the least, one cardinal factor which plays the basic role in leprosy control is the para-medical worker. He should be encouraged, properly motivated and better trained to be able to cope up with the responsibilities entrusted to him. Periodic refresher courses to bring the para-medical worker upto date with the latest information about leprosy and other scientific advances having bearing on public health should be conducted.

TABLE 1

SLUM SURVEY I

Population		Male	Female	Male children	Female children	Total
Enumerated		92,038	82,052	67,336	62,801	3,04,227
Examined		57,842	70,782	60,519	57,842	2,48,348
Percentage of examination		62%	86%	89%	90%	82%
Total No. of Cases Detected, Type-wise & sex-wise	L	123	45	9	2	179
	N	588	884	784	785	3041
	N?L	40	36	26	27	129
	Total	751	965	819	814	3349
		Male adults	Female adults	Male children	Female children	
Prevelance by Age group		1.3%	1.36%	1.35%	1.4%	
		Total males	Total females			
Prevalence by Sex group		1.32%	1.38%			
Gross Prevalence						1.35%

TABLE 1A

SAMPLE RESURVEY

	Old population	Migrated (—)	Per cent	Immigrated (+)	Per cent	Total
Enumerated	10,954	870	7.8%	7,721	43.3%	17,805
Examined	5,520	—		3,846	49.8%	9,366 (52.6%)
Cases Detected	21*	—		50		71
Prevalence	3.8 Per Mille			13.0 Per Mille		7.6 Per Mile

TABLE 2

SCHOOL SURVEY

	No. of Schools	No. of Students enrolled	No. of Students examined	Per cent	Cases Detected L	N	N?L	Total	Prevalence Per Mille
I Survey	353	2,20,245	1,87,325	85	6	1,949	58	2013	10.7
II Survey	346	2,10,455	1,77,583	84	—	1,386	16	1402	7.9

TABLE 3

HEALTHY CONTACT SURVEY
CASES DETECTED

Total Healthy Contacts Registered	L	N	N ? L	Total
28,281	27	609	29	665

TABLE 4

CASES DETECTED AND REGISTERED (Mode Wise)

	Total Cases	Detected %	Total Cases	Registered %
Slum Survey	3,423	27.9%	2,266	21.9%
School Survey	3,333	27.2%	2,768	27.7%
Healthy Contact Survey	665	5.4%	480	4.6%
Voluntary	4,853	39.5%	4,853	46.8%
Total	12,274	100.0%	10,367	100.0%

TABLE 5

IN-PATIENT MEDICAL CARE (Dayasadan)

Number of Patients admitted—Yearwise and average stay

Year	No. of Patients	From Project Area	From out of Project Area	Average Stay in Days
1973	148	93	55	48
1974	175	104	71	42
1975	208	158	50	29
1976	297	282	15	28

TABLE 5A

REASONS FOR ADMISSIONS

Year	Ulcers	Reactions	T.B.	General	Total
1973	76 (51%)	17 (11%)	5 (3%)	50 (34%)	148
1974	125 (71%)	32 (18%)	4 (2%)	14 (8%)	175
1975	139 (66%)	52 (25%)	6 (2%)	11 (6%)	208
1976	154 (51%)	111 (39%)	3 (1%)	29 (9%)	297

TABLE 6

SALIENT FEATURES
CASES DETECTED

Name of the projects	Population covered	Slum Survey	School Survey	Voluntary Survey	Contact Survey	Total
Greater Madras Leprosy Treatment & Health Education Scheme, Madras Started in 1971	16,00,000	3,423 27.9%	3,333 27.0%	4,853 39.5%	665 5.4%	12,274 100%
Greater Visaka Leprosy Treatment & Health Education Scheme, Vishakapatnam Started in 1975	5,00,000	465 16%	698 24%	1,534 52.7%	213 7.3%	2,910 100%
Greater Calcutta Leprosy Treatment & Health Education Scheme, Calcutta Started in 1975	1,60,000	273 28.0%	123 12.7%	557 57.5%	16 1.6%	969 100%

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LEPROSY REHABILITATION: A PROBLEM IN SOCIAL WELFARE

S. D. GOKHALE

Historically, Leprosy had been one of the most dreaded diseases afflcting mankind. It was disfiguring, disabling, and eventually fatal and since without scientific treatment, its contagiousness remained unchecked, segregation of the leprosy-afflicted was the only recourse left to the society. Now with the discovery of life-saving drugs, leprosy is no longer the dangerous and crippling disease it was. However, the old attitude and prejudice die hard, leading to continued avoidance and separation of the patient which is not only inhuman but militates against effective detection and early treatment. It is therefore that the leprosy patient needs to be viewed with a special consideration and treated with a sense of dedication due to a much-maligned victim.

REHABILITATION AND ITS APPLICATION TO LEPROSY :

The word rehabilitation has been in use for many years in connection with persons handicapped from causes other than leprosy. Its use in leprosy work is comparatively recent. In applying 'rehabilitation' to this work, however, a distinction between leprosy-handicapped and other handicapped persons, has been overlooked. Whereas most handicapped persons are not normally viewed as social outcasts, there is tremendous ostracisation of the leprosy patient. Because of this inherent distinction between the latter and other handicapped people, the process of rehabilitation must take into account the basic differences, both social and psychological, between these two groups. Since handicapped people are not usually considered as outcasts by society, the question of social acceptance does not arise in their rehabilitation. The blind, the deaf, the mute for instance, are considered different from the able-bodied but remain in their own homes, vocations and society in general. But leprosy patients are uprooted from their social milieu and a process of dehabilitation keeps step with the disease.

REHABILITATION OF THE PATIENT :

There are two main aspects of rehabilitation (1) Reestablishing the economic productivity of the patient and (2) re-assimilation in society. Without either of these, the rehabilitation is incomplete.

In this respect, it is pertinent to recall the definition formulated by the Second Leprosy Expert Committee of the World Health Organization, viz :

'By rehabilitation is meant the physical and mental restoration as far as possible, of all treated patients to normal activity, so that they may be able to resume their place in the home, society and industry. To achieve this. treatment of the physical disability is obviously necessary, but it must be accompanied by the education of the patient, his family and the public, so that not only can he take his normal place, but society will also be willing to accept him and assist in his complete rehabilitation.,

This WHO definition does not fully bring out the need for social assimilation as a necessary complement to economic independence. Further, it must be recognised that if the former 'lepers' are settled as a separate group away from society, and vocations are provided to them there, they can only be considered as 'Vocationally settled', but not as rehabilitated'.

SOCIAL AND PSYCHOLOGICAL EFFECTS OF LEPROSY :

It is difficult to analyse the traumatic experience to which the leprosy patients are subjected, and the tremendous changes that take place not only in the body but in the

mend, nay, the whole gamut of emotions and feelings of the patient. The shock of leprosy is received by the patient as a psychological trauma. A small unnoticed patch on his body, once medically diagnosed as leprosy, envelopes the patient with the cumulative feeling of helplessness, shame, and dependency. The problem is further complicated since the patient has little medical information about leprosy. He has heard about it, the image that is created in his mind is of a person who has lost his limbs, whose face has been deformed, and who is totally dependent on the tender mercies of society. Consequently, he starts considering himself as a potential outcast, who will eventually lose his arms, his nose, his fingers and be forced to join the mobile tribe of faceless numbers suffering from leprosy. Because of this, his initial response is to hide the disease, and he is not willing to attend a clinic for treatment, with the result that the disease grows secretly, adding in turn to the social fear, inferiority and helplessness experienced by the patient. This affects the patient's personality and behaviour pattern adversely, and in a few cases, even contributes to anti-social conduct.

SOCIAL AND ECONOMIC OSTRACISM :

As soon as society knows that a certain person is suffering from leprosy, the process of outcasting starts. A social distance is created between the patient and society. This affects not only the individual patient but also his family, and is experessed in many ways. Patients are not invited to religious functions, social ceremonies, community occasions. They are refused admission to educational institutions., public transport and communication, places of employment, etc. Also usually marriage with a leprosy patient is avoided. The life of a patient who is thus outcast is a continuous process of social persecution resulting in social death which, in all likelihood, is more cruel than physical death. As these patients cannot participate in the social and economic activities of the community, they tend to become isolated and parasites, dependent entirely on charity. These factors together create a new gestalt of their personality and behaviour, expressing itself in a bitter, asocial but not anti-social, and complex manner. The personality of the patient tends to be like an iceberg where the major portion is not visible ; what is visible is not complete. This inevitably complicates the problem of rehabilitation.

VARYING DEGREES OF STIGMA :

The socio-economic stigma on leprosy tends to vary in intensity in accordance with the type of society., country, and community. Even within a single country, as for example India, social stigmatization appears in varying degrees in various parts. The tribals do not know much about leprosy in medical terms, and therefore in some respects they are less fearful of it. For the educated white-collared urban society, social stigmatisation is more intense and acute. This difference is also visible in town and country. The degree of stigma also depends on the prevalence of the disease. In those areas where the prevalence of leprosy is high, with patients found in many homes, the stigma is generally less marked than in regions where the prevalence is low, and patients are to be found in very few homes. Ostracism may also vary according to the impact of the disease. In some areas, only patients with gross deformities may be ostracised while in others, even an early skin patch could lead to ostracization if it becomes known. Finally, the degree of stigma will depend considerably on the patient's occupation. Generally, agricultural workers are not dehabilitated as easily as white collared worker.

REHABILITATION ACTION FOR THE PATIENT :

The extent and type of rehabilitation action necessary depends considerably on the degree of stigma that exists in the community, the previous occupation of the patient and related factors as indicated above. Some of the crucial areas of action aimed at the rehabilitation of the leprosy patient are outlined below.

Education of the community : Since rehabilitation consists of retaining in, or returning the patients to, it is essential to prepare society to receive them. To this end, educational programmes on leprosy must be started and pursued on a sustained basis. The existing structure of the anti-leprosy service should be used, and, strengthened as necessary, for promoting this campaign of education and information.

The education of employers and employment sources is equally important. If the patients are denied the opportunity of economic participation, or are driven out of their vocation or employment because of their disease, a class is created which is exploited

economically and unsatisfied socially. On the other hand, it is observed that patients, even in a severe stage of leprosy, are not affected by stigmatisation if they are not dependent on society economically. Economic independence often provides a kind of protection against stigmatisation. Therefore, if the patients are to be saved from stigmatisation and social distance, every effort must be made to retain them in their own employment of occupation. If this is not possible, retraining should be provided so that they can be established in vocations similar to their previous ones. Except for patients who are so old or disabled that they are incapable of economic activity, every other patients must be provided with an opportunity to participate in economic production. This is an extremely important part of rehabilitation.

COMBINED DETECTION AND PSYCHO-SOCIAL TREATMENT :

As increasingly accepted, the earlier taboos imposed by leprosy on the patient must gradually give way to a systematic understanding of the total needs of the patient. An appreciation of the overall milieu surrounding the patient could result from an analysis of his home circumstances (including the family structure, its economic status and the extent to which this depends on the patient), the community's attitudes to the patient (including the extent and type of stigma prevailing), the personality and ability assessment of the patient (especially his work-potential and re-training needs), etc. In such a comprehensive approach, naturally various disciplines (such as doctors/nurses, occupational therapists, physio-therapists, psychologists and social workers) will need to work hand in hand.

The detection and after-care processes must also be strengthened in a way that encourages the patient to overcome his fear of diagnosis and detection. Often patients are observed to be unwilling to go outside the family either for treatment or for training. Often because of the stigma, the family helps to hide the disease, and the patient is not very alert about his treatment. This accounts for an apathetic attitude resulting in serious long-term deterioration, for the patient as well as for the community. Detection must therefore try to encompass these vast apathetic numbers of those affected by leprosy.

LEPROSY, ITS PREVALENCE AND MAGNITUDE :

In the XVIth session of the National Sample Survey, an estimate was made of the population of leprosy patients. This data seems to be more indicative than complete. As far as Maharashtra (a state in India) is concerned, there are 77,000 families which have at least one disabled person in the family. Out of these, 70,000 families, or 90% of the units, are in rural areas. In other words, in the state of Maharashtra in 1.1% families, there is a person suffering from some kind of handicap. In rural areas the incidence of disability is 1.4% while in urban areas it is 0.34%. The total population of disabled in the state of Maharashtra is 81,000 of which 73,000 or 90% are in rural areas and 8,000 in urban areas. This indicate that for every 10,000 persons in Maharashtra state 23 persons are disabled. In rural areas this incidence is 25 per 10,000 and in urban areas 8 people in 10,000. Within the disabled group, the largest number consists of blind people followed by the leprosy-affected. In Maharashtra state 95% of these are in rural areas. The estimates in the National Sample Survey therefore would appear to be less than realistic for two reasons :

(a) The basis of the sample survey is a household, while a number of patients are either not living with their families or are institutionalised ; these have not been taken into account.

(b) There are a number of patients who are not identified or detected through the Survey, Education and Treatment Centres, (SET Centres) Campaign.

Regional Variation : Regional variations in leprosy make for an instructive analysis. In an urban milieu, it is possible for the leprosy patient to remain anonymous ; he therefore chooses to come to urban townships. However, the majority of the patients are still in rural areas. The prevalence of leprosy varies from state to state. In some villages in India, it is as low as 2 per thousand. With the spread of the Survey, Education and Treatment movement, a number of SET centres and leprosy control units have been established.

Whether a patient is in an urban area or in a village, the intensity of his disease does not change, but with the changing social and economic context the problem of rehabilitation does change. In an agricultural country like India only a minority of patients are

employed, self-employed or are in trade or industry. In this context, it is tragic that for patients employed in some occupations, social stigmatisation is quick and intense. For example, a labourer in a factory, a teacher, a nurse, a person running a provision store or a dealer is very often quickly stigmatised because of leprosy, stigmatization may occur more readily in the atmosphere of a city, but in rural areas where it may take a long time to stigmatise, the process of recovery is equally prolonged, since attitudes in rural areas are hard to change.

SOCIAL WELFARE AND LEPROSY REHABILITATION WORK :

Before introduction of sulphone drugs, leprosy work was undertaken primarily by missionaries, by the kind-hearted but untrained volunteers. These workers undertook a tremendous task. The scientific approach to rehabilitation is of comparatively recent origin and provides the framework within which to identify the role of social welfare. Leprosy and its treatment is primarily a medical concern whereas rehabilitation is primarily a social welfare concern. While leprosy work was limited to closed institutions and settlements, rehabilitation also had a limited meaning. In the new approach, as patients are encouraged to stay in their own society, the rehabilitation tasks have undergone some changes resulting in a greater need for professional social work. Medical advancement afforded a new parameter in this connection. Thus, whereas previously there was little possibility of being cured of leprosy, the number of cases in which disease is controlled or burnt out is now on the increase, creating a special problem of rehabilitation of negative but disfigured cases. Previously, if the patient entered an institution he had no alternative but to spend his entire life there, but patients now can and, do come back. It is therefore desirable for the institutional authorities to retain patients in the institutions for as short a time as possible. Even patients staying in independent settlements have to be encouraged to come back to society. These developments have given a new dimension to the role of **professional social works** in rehabilitation of leprosy patients. Social workers can contribute particularly in the assessment of the personal and home circumstances of the patients, in community education, social adjustment, employment counselling and aid, and overall influencing of social attitudes to the patient. They also have a major role to play in the areas of after-care and follow-up. with adequate non-institutional services, social workers can also contribute by undertaking applied research to test out the impact of current programmes. Their findings can be useful in planning prospective action in leprosy rehabilitation work.

SOME PRINCIPLES :

In applying techniques of social welfare to rehabilitation the following principles should be kept in mind :

(a) Social work is to be treated as a profession, and in planning rehabilitation, a scientific approach should be adopted which should suitably draw on the tools of research analysis ;

(b) Workers such as doctors, nurses, occupational therapists and physio-therapists involved in rehabilitation should be oriented to the contribution and tools of social welfare. A similar orientation should be given to paramedical workers, social welfare aides and voluntary social workers ;

(c) Whereas leprosy rehabilitation is taught at present as a part of Indian social problems in the social work curriculum, a separate course should be developed on 'rehabilitation'. Through this, social workers and others should be given information about treatment methods such as medicines, occupational therapy, physiotherapy etc.;

(d) As it does not seem likely that trained and professional social workers will be available in adequate numbers in the near future, maximum use should be made of volunteers and social welfare aides after giving them adequate orientation.

TYPE OF LEPROSY INSTITUTIONS :

Leprosy institutions are known by various names such as instituions, homes, hospitals, asylums, infirmaries and shelters. These names are often used interchangeably. There are also what are known as leprosy settlements ; these are voluntary, and patients join these without compulsion. There is no restriction of movement and there is no organised institutional life in terms of nutrition, vocation, training etc. Usually, the whole family joins a settlement as a unit. In an institution, life is much more regulated, as time-tables, scales of clothing and diet etc., are imposed. The agency is managed by

authority, and inmates have no participation in policy-making and management. It is also observed that institutions are not always oriented to one purpose such as medical treatment, vocational training, hospital function etc.; they are often known to operate as multipurpose institutions. In a developing economy, high specialisation is not always possible. Consequently some institutions operate partly as a hospital, partly as an infirmary and partly as a shelter.

For proper planning of rehabilitation, it is considered advisable that the institutional set-up be carefully assessed with a view to expanding its rehabilitation potential. A brief review of each institution-type is offered below :

(a) *Leprosy hospitals* : These are institutions where patients, who need to be medically observed and attended to come for medical treatment. Their duration of stay in the hospitals is limited to the period of medical treatment.

(b) *Asylum* : These are really for segragation, convalescence and treatment. With the introduction of domicillary treatment, the need for asylums is likely to decrease.

(c) *Infirmaries* : These are for patients who are disabled, infirm and cannot look after themselves, including their hygiene.

(d) *Shelters* : These are institutions where able-bodied patients can come if they are homeless of if they have been thrown out by society. The shelters provide food, clothing, shelter and opportunity to work and earn.

In considering the above four categories, we find that the need for medical aid is highest in the hospitals, and lowest in the shelters. As the need for medical treatment diminishes the period of stay of the patient increases. Therefore the present need in the field is to modify the institutional setting so that rehabilitation can be meaningfully included in the work programme of each institutional type. Another set of institutions are comprised of leprosy settlements, villages and islands or free colonies. These are discussed below :

(1) *Leprosy settlements* : Also known as colonies, these are found all over Asia. While every effort is being made to disolve these settlements and absorb the patients in society, patients are often observed to be rather reluctant to leave, primarily because of stigma, or because of the freedom they enjoy in a settlement. Starting new settlements or exclusive communities of the leprosy-affiicted should nevertheless be avoided as far as possible. Such centres contribute to perpetuation of the stigma of the disease, and do not help to change the age-old outlook of society towards leprosy-handicapped persons. Owing to their wide prevalence, however, the main features of settlements may be briefly discussed, with a view to reorienting their rehabilitation.

Firstly, they resemble normal communities except for the fact that they are predesigned for segregation. The inmates are free from the restrictions of institutional discipline and custody and have independent houses, where they can cook for themselves, follow and choose economic pursuits along with their families. Further they are free to leave at will.

Secondly, the principal work in these settlements is usually agriculture, even though from the medical point of view, this occupation may not always be suitable, especially for patients with anaesthetic limbs. This is because alternative employment is not readily available, even though many disabled patients may be physically fit to do other kind of work.

Thirdly, if agricultural work has to be one of the principal activities in the settlement, this should be located where enough good, well-watered agricultural land with good access by road is available. With good planning, use of modern agricultural methods, chemical fertilisers and efficient organisation, the land can produce enough food and even other cash crops. Associated with agricultural work, suitable small industries for allied products with easily available markets should also be started. Thus the settlements could become agro-industrial projects and eventually attract other handicapped persons and even normal people if they are unemployed. In promoting this activity, full measures should be enforced for safety of the agricultural and industrial products sold to the public.

Fourthly, apart from agricultural land, a heavy initial investment is required in a settlement for housing, reclaiming the land, equipping the houses and purchasing implements, vehicles etc. Besides this, it would also be necessary to spend for the maintenance of the inmates for the first few years until the

settlement becomes self-supporting. The success of such a project, however, depends on many factors, of which the more important are the soundness of the scheme, the capacity of the organizers, and above all the motivation of the settlers. A settlement started without these essential requirements is very likely to be a failure.

Fifthly, as settlements are residential centres with inbuilt facilities for employment, their inmates cannot be considered as rehabilitated. It is therefore desirable to try to find employment in society for the residents of these settlements, so that they can return to society. In this direction, the organization of cooperative societies of leprosy patients may be a suitable supplementary measure. The cooperative societies, while retaining individual freedom will at the same time provide a new opportunity for collective action, and share the fruit of their labour without exploitation. Such cooperation may be encouraged in settlements as well as outside.

(2) *Leprosy villages* : As in case of settlements, the leprosy villages, whether predesigned or evolved, cannot be credited with real rehabilitation as they foster a segregated existence. Further, villages which are not pre-designed generally amount to congregations of patients who have not been able to be economically self-reliant or to be absorbed in the normal community. This often results in substandard living in such villages, verging on slum conditions. Some adherence to minimum social standards and provision of protection and care is therefore called for to make them more akin to the level of functioning of a settlement.

(3) *Island colonies* These are maintained by the State agencies primarily for isolation of patients. They depend on the mainland for supply of food and other materials while patients earn their living to a certain extent through farming, cattle-raising and fishing. Efforts are often made to close these colonies and bring the patients to the mainland, but this has not been achieved so far. Island colonies are also developed in U.S.A., Philippines etc.

As treatment and rehabilitation programmes develop, the need for all other institutions except hospitals (for purposes of treatment) and rehabilitation centres (for training) will be reduced. It is actually the duty of the state and the obligation of an enlightened society gradually to reorganise the prevailing institutional set-up and rely more on action that will generate new opportunities of life for the patients.

PLANNING LEPROSY REHABILITATION

The task of rehabilitating approximately 30,00,000 leprosy patients in India can only be undertaken through a systematic and planned approach and with a well-conceived legal framework. The legal and planning aspects are discussed below.

Leprosy and law : Most countries have some legislation on leprosy. Some laws relate to compulsory segregation, some to use of transport, some to the presence of patients in public places and some to divorce and such other aspects. These laws, enacted in the distant past, when the attitude of the State and society towards leprosy patients was very harsh and there was no discrimination between infectious and non-infectious patients, were designed to be primarily in the interest of the general society. Some of the countries which had legislation for compulsory segregation have now given it up. But in many countries the other out-dated and unnecessarily harsh laws are still not repealed, though they are no longer implemented rigorously. Of the countries which have no compulsory segregation, some have a public health act authorising district health authorities to segregate infectious patients when they consider this necessary.

Both leprosy workers and lay people want leprosy legislation, but for opposite ends. The former would like to repeal outdated legislation and replace it by new laws, primarily to protect the leprosy patients from the unjust attitude of the State and society, and also to give them the same rights as any healthy citizen. On the contrary, the lay people want legislation to exclude leprosy patients from normal society.

In democratic countries, it is the elected representatives of the people who decide whether legislation should be enacted. Even legislators with progressive attitudes may not have scientific orientation on leprosy. It may therefore be inopportune or even dangerous to repeal, modify or replace legislation without educating the legislators. The question of repealing should be raised only when there is evidence that the legislators' attitude and thinking about leprosy have changed and they are well-informed.

The Technical Committee on Education and Social Aspects of the VIIIth International Congress on Leprology, held in Brazil in 1963, has made the following recommendations about legislation :

'In the light of modern knowledge, there is no need for special legislation on leprosy, and any legal measure dealing with leprosy should form part of general public health regulations. Wherever there is legislation on leprosy that is not in conformity with the modern approach to the disease, Government should be urged to revise such legislation suitably. It is recommended that Governments still enforcing compulsory segregation, abandon this policy'.

In India, the Leprosy Act was passed in the late nineteenth century. In every respect it is out of date and out of context, and it is desirable to review and amend it, keeping in mind the above mentioned considerations. The importance of well-conceived legislation for fostering an overall climate conducive to the treatment and rehabilitation of the patients cannot be overstated.

STATISTICS AS A BASIS FOR PLANNING :

To plan rehabilitation work of such a magnitude, some estimate of the treatment and rehabilitation needs of the target population is necessary. Indicative data can be gathered from programming and planning purposes, by classifying the patients into viable sub-groups of categories, viz :

(a) Institutionalised patients.

(b) Patients attending outpatient clinics.

(c) Sufferers who are undetected and unregistered.

(d) Beggars and mobile groups of leprosy patients.

Estimates of the population in each group and their respective needs will provide a suitable basis to plan for their rehabilitation.

Institutionalised patients : Patients approach leprosy institutions with different motives which make an impact on their medical needs. Thus, some patients regard the institution as their permanent residence and have no desire to go out. They are therefore likely to neglect their medical treatment. Other patients go to the institutions as a last resort, and feel a keen desire to return to the community. These patients are likely to be careful about their treatment. Those who are completely disabled or infirm, who cannot return to society, and who are viewed as terminal cases, require long-term attention, which is not always feasible within the institution. In some countries therefore experimental attempts are made to keep terminal cases in families by giving them grant-in-aid. Finally, there are patients who after treatment in institutions become non-contagious or 'burnt-out' cases. Yet since many of the institutionalised patients have no contact with their families, they have no home to go to, and are therefore in real need of rehabilitation.

Patients outside institutions : Patients who come to out-patient clinics can take care of themselves, and their rehabilitation needs are limited. They probably need some financial assistance to start a small business or to reorganise their vocation, or to buy some basic equipment, or perhaps they need an introduction. If a rehabilitation worker analyses these cases, he will find that even in this category there are patients who are in the process of dehabilitation.

Undetected patients. Patients who are not registered or who are not detected by the Survey, Education and Treatment (SET) Centres have different problems. The number varies from State to State depending on the status of leprosy work in each. In some countries there are fewer number of undetected cases. Unfortunately in India this is not the case. It is estimated that there are many undetected cases and therefore the primary aim of all SET work is to detect patients and, on detection, analyse their rehabilitation needs and then provide for medical assistance.

Leprosy beggars : Beggars per se are a social problem ; patients who are driven to begging are normally not a large group statistically, but since they exhibit themselves on the foot-paths they become targets of attention for everyone with a social concern. Since they are mobile, it is very often difficult to find out the exact number. However it is now agreed that begging is primarily a social problem, not a medical one. Because the leprosy-affected begger suffers from two stigmatisations, both as beggar and as leprosy patient, he gets isolated for fear he might spread the disease. Therefore the question of rehabilitating leprosy beggars should primarily be a subject of correctional administration, and not of public health.

PROGRAMMING CONSIDERATIONS :

For successful programming of rehabilitation a continuous social, economic and psychological study of the patient (s), is essential along with a systematic case detection campaign. To this end, and while planning for rehabilitation programmes, the following considerations should be kept in mind :

(a) The case detection campaign should be spread far and wide along with community education, research and man-power training.

(b) Rehabilitation should be planned for the patients who need it most. The basic criteria for rehabilitation, namely assimilation in society and economic independence, should not be compromised at any cost.

(c) Rehabilitation training centres should be established with special arrangements for vocational training. In selecting the vocation, rehabilitation considerations should combine with medical considerations.

(d) Sheltered workshops should be established.

(e) SET surveys for case detection, education, and treatment should be undertaken simultaneously. In every country where an SET programme has been developed the incidence of disfigurement and disability has been reduced. Timely medical treatment has helped patients to control the disease without being affiicted by disability or being dehabilitated. This campaign overcomes the fear of social stigmatisation. The low per capita expenditure of the scheme, and the high success percentage in results undoubtedly prove that this is a cheaper method of dealing with leprosy than institutionalization. Therefore this scheme should be given priority over any other programmes.

Rehabilitation potential among patients : In making such plans, the rehabilitation potential of all the patients should be assessed. For this purpose, the following factors have to be taken into account :

(a) Attitude of the patients towards rehabilitation.

(b) The personality traits and behaviour of patients.

(c) Social attitudes of the patients.

(d) Desire to learn skills.

(e) Stability of mind, need for steady work.

(f) Over-all appearance of the patient from the point of view of social acceptability.

This assessment will help to identify the major obstacles to rehabilitation of the patient, and how they can be removed.

Occupational choices : While deciding what occupation or vocation should be given to the patient, medical factors have to be taken into account. Patients who have lost or have benumbed extremities naturally have many limitations in this area. For purposes of planning rehabilitation, patients could be categorised on four medical grounds :

(a) Patients who are not disfigured or whose hands and feet are not anaesthetic. These can be given a variety of work to handle.

(b) Patients whose hands are anaesthetic, but whose fingers are not lost. This category of patients should be given work in which they will not come in contact with hot, sharp or rough edges. If essential, the handles of the tools should be rubber-coated.

(c) Patients whose hands are anaesthetic and also damaged to some extent. These should not be given any work involving pressures or strains, for example, handling small and sharp parts of a machine, a watch, handling small screws etc. For such patients, different work has to be found or tools have to be changed.

(d) Patients whose feet are anaesthetic have to be provided with special footwear, and should not be asked to undertake jobs involving much standing.

Whatever the type of work that is found for a patient he should be able to get a minimum wage to sustain himself. In offering work opportunities, the ability and preparedness of the patient should be taken into account. If the patients undertake work which is beyond their physical capacity, they will soon become chronic dependents. For housebound patients work should be found which can be done at home. Only those who cannot find employment in the common market, should be sent to the sheltered workshops ; otherwise preparation and training should be completed in the normal training centre for the normal community.

EVALUATION :

There are many ways of measuring the effectiveness of the programmes. One is to measure the incidence of disfigurement. When rehabilitation work first started in Maharashtra State, about 30% of patients were disfigured (1952), but now the figure is 10%. The incidence of disfigurement in a ten year period ending in 1971 is given below :

1961	52.9%
1962	42.8%
1963	55.3%
1964	45.4%
1965	50.4%
1966	35.2%
1967	32.8%
1968	6.3%
1969	20.8%
1970	4.6%
1971	6.8%

It also appears that the public attitude is changing about reporting leprosy. Previously every patient had to be detected. Now more than 40% of patients report on their own.

The categorisation of patients is also changing fast. The nodular type of lepromatous patients are rarely to be found. Many of the patients are of indeterminate category, or of tuberculoid category. The proportion of lepromatous cases (which is known as L rate) has been observed to have diminished considerably in the last few years as is evident from the following :

1961	27.6%
1962	21.8%
1963	40.9%
1964	39.3%
1965	40.0%
1966	21.5%
1967	40.9%
1968	30.7%
1969	17.1%
1970	5.4%
1971	10.2%

Additional indicators for assessment of the impact of the various programmes of course need to be developed. These should help improve future performance and viability of programmes in the area.

CONCLUSION :

Major head-way has been made towards tackling the problem of leprosy. S. E. T. (Survey, Education and Treatment) centres have been started on a wide scale. Custodial care of the patient has been given up in favour of domiciliary treatment. Much hard work is going on in the effort to fight this malady. The base of the problem being very broad, the result does not make an appreciable mark but its intrusive impact should not be lost sight of.

VOCATIONAL REHABILITATION OF THE LEPROSY AFFLICTED

C. ANTONY SAMY

INTRODUCTION

Leprosy is a burning problem in India and in a number of less developed countries in Asia, Africa and South America. World bodies concerned with the health of the people and the governments are also concerned about this and are making concentrated efforts to control, and if possible, to eradicate the disease. After more than a hundred years, after the bacillus has been identified, and colossal amounts of expenditure, control seems further away and eradication a dream that cannot be fulfilled. So, simultaneously efforts are being diverted towards purposeful rehabilitation and relief of the leprosy afflicted. Vocational rehabilitation which comes at the end of the spectrum which starts with the medical work is the ultimate goal. Medical treatment and surgical correction should ultimately lead to vocational rehabilitation which would make the person independent and selfreliant.

CLASSIFICATION :

The leprosy afflicted are generally classified according to the bacteriological status which is useful for medical purposes. However, for vocational rehabilitation a different system is more meaningful.

1. Those with only patches and having no deformity.
2. Those with minor or correctable deformity and partial anaesthesia of the limbs.
3. Those who have totally anaesthetic limbs and severe deformity or loss of limbs.

The first group can be integrated into open society without much difficulty. Those who have very severe deformities and who are very old are to be looked after by their families or special homes and it is the middle group who would benefit most by rehabilitation programmes.

Attempts have been made to standardise definitions and measure deformity. While it may be necessary for a theoretic, scientific study, for practical purposes in rehabilitation, these can be general guidelines since a more important factor viz. motivation, would be the overriding element.

They can be further classified according to age, sex, and skills possessed, educational levels and whether they are rural or urban based.

THOSE WHO NEED REHABILITATION:

By and large, the majority of the leprosy afflicted are in rural areas and those found in urban centres have migrated from rural areas. Most have had no education or skills and the vast majority of them are over twenty years of age.

There is a perceptible stigma about leprosy. But fortunately, compared to the vast number who are afflicted by the disease, those who are ostracized are not many. The social customs prevalent in the rural society do not very much affect the leprosy afflicted, excepting those with gross, disfiguring deformities. They may not be able to eat in hotels or visit all places freely ; but in their own homes, they are tolerated if not accepted. Those who have some income manage to live fairly comfortably in their own villages. Thus those who need rehabilitation fall into two major groups :

(i) Those who have, due to social stigma or economic reasons, migrated to the cities, and have taken to begging. Their's is more a social problem than a problem of leprosy.

(ii) Those who suffer a handicap because of the progression of this disease. This group can be further classified into :

   (a) Those whose occupation becomes hazardous due to the effects of the disease e.g., a goldsmith or blacksmith with anaesthetic hands.

   (b) Those who can be productive but are isolated because of the disease.

The majority of the leprosy beggars are beyond the means of any meaningful rehabilitation. Many of them have survived long periods on doles and cannot contain themselves to fixed work situations.

RURAL OCCUPATIONS :

As indicated earlier, the majority of the leprosy afflicted come from rural areas, with agricultural background, have had very little education and no specific skills. For such people rural based cottage and small industries which do not demand high skills, complicated marketing, much capital or working costs will be the answer. The rural occupations can be in

1. Agriculture.
2. Crafts and arts.
3. Rural based small industries.

AGRICULTURE :

In agriculture, certain operations like wet puddling may be difficult. Labour intensive horticultural work will be advantageous. Production of hybrid seeds involving manual pollination, sericulture which needs mulberry cultivation and frequent harvesting and such work will be very paying and at the same time can be done with very little training.

CRAFTS AND ARTS :

Crafts and arts are generally traditional work. Children follow parents doing such work and different areas have become famous for certain type of crafts. Weaving in Conjeevaram, potteries in Rajasthan, mud toys in Andhra are specific examples of such work. But weaving of mats and cloth, chalk making, rope spinning and toy making do not give high wages.

RURAL BASED SMALL INDUSTRIES :

Rural based small industries are not only an avenue of employment but they can help the development of rural areas. Small carpentry or smithy units making simple furniture, ploughs and agricultural equipment can be paying and help introduction of better agricultural practices. Designs are available from research centres and can be copied. Silk thread extraction from cocoons, bangle making, production of simple aluminium utensils are other areas of employment. Poultry and small dairies can also be kept.

Compared to industrial rehabilitation, work such as these, has the advantage that people can be easily trained to do such work and in a short time, and they are not expensive to set up and operate. The greatest advantage of such schemes is that the people involved in such work can remain in their own homes and maintain the existing relationship with society. However, the disadvantages are : the units will suffer and even close, if the leaders of the units do not have entrepreneurship, and good marketing abilities. Even then, the economic gains to the involved individuals is not high. But then they are to be compared with others in the rural areas who also have a very low per capita income.

INDUSTRIAL REHABILITATION :

With the growth of large, medium and small-scale industries in the urban, and semi-urban areas, industrial rehabilitation is a very good avenue for employment. This is particularly advantageous to those leprosy afflicted who are young and who have had some education. In most industries there are a number of unskilled and semiskilled occupations, which can be taken up by these people.

Most jobs in industries can be filled by the leprosy afflicted and there is no limit to what jobs they can hold except that the work should not involve extra risks and should avoid any further damage to their limbs. By and large, work such as glassblowing, working with molten metal and handling of abrasives are to be avoided.

While most positions can be filled by the leprosy cured, to reach well paid jobs they should be taught some skills. Trades such as mechanical or civil draftsman, turner, miller, machinists, inspection area, are some of the

specific positions that can be filled even by those with some deformity. So training in these areas will help them.

EDUCATION AND TRAINING :

Care should be taken to make sure that the education is not interrupted because of the onset of the disease. Basic education would help them to get formal training which can lead to successful rehabilitation. For those whose education had been interrupted special coaching can be given in languages and arithmatic, which can be followed by industrial training.

Industrial training can be formal like those imparted in Industrial Training Institutes or informal, on-the-job training, which can be short and may be sufficient for most jobs. Formal training is prolonged and can be expensive. Most Industrial Training Institutes, unless manned by sympathetic people, would not admit physically handicapped people. Even if they admit the leprosy afflicted, they would not get the special understanding to tackle mostly psychological problems. So it becomes necessary to start special Technical Training Centres for the leprosy afflicted. However, care must be taken to see that these are not centres of isolation, but must aim at integration and so should admit other handicapped people. In choosing areas of training and the persons, the following factors are to be considered :

(1) Areas of training should be such that employment opportunities are available. Training in textile equipment will not be a wise choice in an area where there are no cotton mills.

(2) The persons chosen for training must perferebly be young and must have high motivation to be employed and be prepared to subject themselves to regular work habits. Training elderly people who had been begging for many years or who have spent long periods in sanatoriums are very unlikely to be successful.

(3) Area of training should be such that the resultant employment should not expose them to more risks for their limbs. Typical example would be areas of high temperature working where anaesthetic limbs can be damaged.

PLACEMENT AND FOLLOW UP :

In our country where unemployment and underemployment is rampant, placement should be followed with care. Training would be a waste if it is not followed with proper placement. Both the employer and the employee should be prepared well. Too rosy a picture of the capabilities of the handicapped should not be painted to the employer ; and the employee should be told not to expect any special treatment since most industries will not bother to make any special arrangement.

The initial period of three to six months are very critical since in a new place the new entrant would see even small problems magnified many times. Till they make new friends and adjust themselves to the new situation, they must be helped by a counsellor with frequent visits, and by both advisory and monetary help.

SHELTERED WORKSHOPS :

For those who are badly deformed and those who cannot be employed in open industry, sheltered employment can be tried. Sheltered employment need not necessarily mean subsidised employment for substandard workman. Sheltered workshops specifically for the handicapped have been running successfully as economically viable units.

The A.P.H. workshop in Bangalore, C.B.H. workshop in Aramboly, "3R" workshop in Bombay, ORBIT centre in Tiruchirapalli and the WORTH centres in Katpadi and Tiruchirapalli are ample demonstration of successful rehabilitation light engineering industries.

These industries work as ancillary industries to bigger units and thus solve the marketing problem. But they have the disadvantage that they need qualified managerial personnel and costly machine tools. Viewed as investment per person employed, they are much more expensive to start and run compared to simple crafts. But then the employees earn a much higher salary. A very important contribution that they make is the demonstration of the employability of the handicapped in skilled jobs. Industrialists and employers visiting these centres feel convinced of the capabilities of handicapped persons and offer them employment.

SELF EMPLOYMENT :

Self employment offers yet another avenue. This has a wide potential since varied positions are open. From a small vegetable stall involving a few rupees investment every day, to a huge repair workshop, there is a wide range to suit people with various abilities, skills, and economic levels. Small shops selling cigarettes, toilet articles, cycle repair shops, radio and television service centre, plumbing work, carpentry, cycle rental business, laundry, poultry unit, operating a circulating library are some examples. The investment needed for starting most of these is not high. But entrepreneurship is a valuable trait, if the business has to succeed. If a person is self-employed in an area in which he or his family has some experience and if there is a demand for such a service in the place where he sets it up, chances are it will succeed. The other advantages of self-employment are that the person can remain in his own hometown, his family members can help him look after it and that he can choose the working hours.

FINANCIAL HELP :

Financial help for self-employment is available on easy terms. Most nationalised banks give loans of various amounts, depending on the enterprise, at 4% interest. Compared to the 18% interest normally charged; this is a very light load and most banks view handicapped applicants sympathetically.

The Government of India, through the social welfare department helps voluntary agencies with very generous grants to set up rehabilitation training centres and sheltered workshops.

THE BOTTLE NECK :

Those who need rehabilitation are many and opportunities for employing the handicapped are quite wide and financial help is easily available. The important constraint in vocational rehabilitation is the need for qualified and interested technicians and leaders.

Most rehabilitation centres struggle or fail because they are managed by people who are not equipped with the skills needed to manage, produce and market. Very often they are managed by people who do part time work or look after it in addition to their fulltime work as medical or management people. For those skilled technicians who are willing to work, the salary offered is not attractive. The need to train interested motivated managers is great. Actually it is the first step to successful rehabilitation effort.

Rehabilitation centres in India are doing some pioneering work. A number of them are doing an excellent job. From their failures and successes will come more information and more successful units which can provide occupational rehabilitation which will be the crowning effort of all the work that is being done for the leprosy afflicted. They will cover the villages, towns and cities and will include agricultural work, crafts, trades and industry. In fact, vocational rehabilitation will be in all areas where people are involved—since the leprosy afflicted are also people.

A cadre of people, specialising in occupational rehabilitation can be formed by recruiting interested engineers and technical persons and giving them specialised training in the medical rehabilitation, human engineering, production possibilities, marketing and management. Such qualified, trained and involved people would bring about a welcome change in the occupational rehabilitation efforts, which are now feeble and suffers for want of such personnel.

A VIEW FROM THE WINDOW

B. R. CHATTERJEE

The objective of this volume has been, true to the word, opening a window on leprosy for almost everybody with an interest in leprosy to look through, and see. It is not for me to judge, or criticise. I can only thank, and indeed I am thankful, and grateful to all the contributors for laying down a feast for the inquisitive, for the critic, for the learner, and for the uninitiated. Before leaving the window for the viewers, the temptation is irresistible to add some tit-bits, some 'stray thoughts' and comments as my offerings, not particularly caring where they fall and how they fit. I would scrupulously restrict myself to topics I am somewhat familiar with through work and put forward some arguments and logics backed some-times with suggestive evidence with the hope that these will generate further discussions.

In the following few pages I would attempt to highlight some of the issues and problems that need rethinking both in the light of old knowledge, and of new knowledge. Why particularly old knowledge? It does so happen that in the enthusiasm of new discoveries some very obvious facts or possibilities are either forgotten, or so much taken for granted that it almost amounts to forgetting. Take for example the 1898 paper of Schäffer's, eloquently describing, with evidence, the nose as a very logical source of dissemination of M. leprae. The importance of that old finding has now been appreciated in full after the 're-discovery' of the nose and nose-pharynx as a rich source of M. leprae. It is therefore sometimes useful to reminesce in, ruminate and recall some of the old, pioneering studies in medical biology to get leads from, and appreciate the significance of findings that in the light of modern thinking may seem somewhat orthodox or unscientific.

So, it is from this premise that I will dwell into some of the areas of leprology as they stand today, and try to understand any lessons these may offer.

State of the endomicity—As will have been evident from the preceding chapters, we know more about leprosy now than when the mass campaign was launched in different leprosy endemic countries more than two decades ago. But has all this new knowledge helped improve the leprosy situation? Some experts feel that leprosy has actually increased in most countries. While others think there has been an improvement in the situation wherever control work has been carried on with some efficiency, and this is taken to mean a 50% coverage of the population with the registereed patients taking 50% treatment. The SET pattern of work, and in particular, the way it is implemented has come under criticism. In a private conference of the Leprosy Mission's held last year at Singapur, Dr. Paul Brand had made some very pertinent comments on the shortcomings of the programme as it is implemented, and for the benefit of those who do not have access to its proceedings, I am citing some relevant excerpts from his paper with the permission of the Leprosy Mission:

"When TLM/ALM* workers met in Lucknow in 1953 we seemed to know all the answers; .... We looked back in 1953 to the 1930's and the early 1940's and we remembered that those were the days of no hope; .... In the early 1940's the sulphones came along, the 'miracle at Carville' had happened .... It is now 23 years since that meeting (which is about a generation) and today there is more leprosy in the world than there was then .... We have to ask, what went wrong? How is it that there are more leprosy patients today than there were then? We tried to follow the rules.

There were two things that went wrong, I think. .... I would like to consider those two things one by one, rather briefly. .... Because we have certain

* The Leprosy Mission and American Leprosy Mission respectively.

resources of people and money we can either cover 10,000 people very thoroughly, or 1000,00 people less thoroughly, or may be 1 million people just spraying sulphones by helicopter. So what is the level that is appropriate? The level that was most commonly used throughout India was called the S.E.T. programme, and it consisted in survey, education, and treatment.

It was worked out by Dr. Wardekar, with the guidance of the World Health Organization, and was in many ways a very good programme. But it insisted that because it is basically government, and equal treatment has to be given to everybody, therefore it is based upon the resources that are available from the Indian Government, and that is only so much per patient per year, and this is what we can do with that money. .... There was a sombre moment in the late 1960's when WHO did a world survey and found that in India in the average S.E.T. programme the average attendance, 50-60% in the first year, had dropped to 25% in the 2nd year and by the 3rd year not even 20% of the lepromatous cases were attending regularly for their treatment. Therefore, although the sulphone drugs were being made available in the villages, only about a fifth to a quarter of the lepromatous patients were taking regular treatment, although all who had started treatment were still positive. .... The biggest single cause of the failure of world wide leprosy control is simply lack of confidence in the programmes that are available in the field. In those programmes that had the very low attendance by and large there was no central hospital or hospital bed to which the patient could be referred when he had acute reaction or pain or neuritis, or needed extra help. The second reason why leprosy control is not likely to be readily completed and leprosy is not going to be eradicated in our lifetime is this little business of the smart bacilli. Mycobacterium leprae is not as simple as we thought it was, and faced with the challenge of sulphones it has found an answer, and this is the second great problem facing TLM today, and also facing WHO. .... This is a terrible problem, because the cost of treating a sulphone-resistant person is ten times the cost of treating them with sulphones. .... We are facing a terrific new challenge. It is going to require all of our imagination, all of our resources, all of our sense of dedication, all of our sense of priorities, to be able to handle the patients to whom we are already committed in a way that will give them confidence in our method. .... A good programme does not cost more than about three times as much as a poor programme, whereas a programme for drug-resistant leprosy may cost ten times as much. Therefore we are justified in going into it in depth".

It is hard to disagree with much of these remarks but at the same time it must be pointed out that the implementation of the control programme with the necessary input in terms of money and skilled manpower as envisaged by Dr. Brand is possible only in countries with a limited problem. Norway controlled leprosy through a masive effort whose mainstay was isolation. There is no doubt about a qualitative change in the endemicity in areas of India where the programme has been going on for a decade or longer. Whether we want it or not, the back log of cases with ulcers and mutilating deformities are to stay with us until they are eliminated by natural process. The new cases are largely of the non-lepromatous type and, with less deformity. In all infectious disease situations with the progress of the epidemic the susceptibles are eliminated through suffering or death, and the remainder of the population either escape with mild attacks, or none. On the state of endemicity of leprosy in the Philippines, Doull (1) made the following observation: "That something peculiar was going on which had affected the entire community is suggested also by the fact that as the lepromatous type declined a compensatory increase occured in the non-lepromatous form". This was in the mid fifties when control by DDS mass therapy had only begun and could not have contributed to this change. This trend is also apparent in the centres in India where good records have been kept as in Gudyathum, Vairag, Jhalda, Tirukoilur & Polambakkam. It would be interesting to find out if a similar trend is prevailing in areas not hitherto brought under the control programme. At the Fatehpur control unit of the Santhal Pahadia Seva Mandal of Bihar an Assessment was made in 1973-74 of their control work that began in 1955. It was the impression of the assessment team, of which I was a member, that after a very good record of initial work, there was a general decline of the quality of work due to improper supervision and, guidance. The prevalence rate of 18.24 per thousand at first survey done during 1955-59, went up to 29.34 per thousand at assessment survey of 10% randomely selected villages, done during 1973-74. Even so,

the lepromatous prevalence came down from 4.94 per thousand to 2.80, and the lepromatous rate, i.e. proportion of lepromatous cases, came down from 21.3% at survey I, to 8.7% at assessment survey. Notwithstanding the interference of the control programmes, the endemicity is perhaps taking its own slow course. We can increasingly expect more of milder, non-lepromatous disease and less of the virulent, highly infectious, multibacillary forms due to elimination of the susceptibles and a selective influence of the infection on the population. Naturally, in the case of a generally slowly evolving disease as leprosy, it would take decades before such change became perceptible. I am speaking here strictly in terms of the Indian situation.

Another form of qualitative change in the endemicity that is occuring in areas under effective control coverage is evident in the data in the following table. Studies in Bankura by Dharmendra & Lowe, and that in the Philippines by Doull & Guinto established a 4 times higher risk of contracting leprosy for family contacts of lepromatous leprosy as compared to contacts of tuberculoid leprosy. Also, contacts of tuberculoid leprosy had twice as much risk of getting leprosy as a non-contact. The data presented in this table are from our longitudinal study in Jhalda. The Leprosy Mission started its control programme here in the early sixties and the lepromatous and borderline cases have been fairly well covered by the treatment programme. This is clearly reflected in the equal attack rates among nuclear family contacts of L & BL and T & ID leprosy. This means that with a sustained campaign, the transmission can be effectively interrupted.

In India, since the last hundred years or more, due to a gradual improvement in communications, populations that used to be largely confined within their own villages have started travelling and mixing. This process has intensified many folds since 1947. Also, in the olden days, due to far more severe social stigma, there was an in-built mechanism of isolation. This is also changing gradually. The population has grown rapidly and food production has not been able to keep pace with it. Due to a combination of such factors, transmission is probably favoured and I would not be surprised if there has been a real increase of prevalence in India. But as I already mentioned, the situation has been undergoing a qualitative change. The task would be to intensify this process by general, as well as medical and public health measures.

Prophylaxis—Along with the programme for control through mass therapy, the time has now come to seriously think in terms of prevention and the IMMLEP programme of the WHO through co-ordinated work in many laboratories, have started in a big way the search for leprosy specific antigens, either through a culture of M. leprae, or using antigenically related mycobacteria. The objective is manyfolds: diagnostic, protective and curative; there are articles in the volume that deal with these specific topics.

Along with the search for an immunoprophylactic agent, there has been considerable work done on the possibility of using DDS as a chemoprophylactic agent in near therapeutic dosage. The work in India, and elsewhere, again exhaustively discussed in an article here, has established the value of oral DDS as a prophylactic, but only partially,

TABLE*

Incidence of clinical leprosy among clinically normal individuals of Survey I during the two year interval between the two surveys in eight villages according to contact status in Survey I.

	Survey I Clinically Normal	Present & Exam in Survey II	New cases in two years: T & IDL	L & BL	All Cases	Rate %
(a) Contact Status at Sy I						
Nuclear family contacts						
of L & BL	158	128	6	—	6	4.7
of T & ID	466	412	17	3	20	4.9
All contacts combined	624	540	23	3	26	4.8
Non-Contacts	4017	3615	75	11	86	2.4

* Data reproduced from the records of Field Leprosy Research Unit, Jhalda.

and that too, only in children. There is no doubt that children do frequently get infected, but leprologists the world over know that children largely escape with mild, and mostly self-healing lesions. It is safe to assume that these mildly clinical or often subclinical infections are immunising infections in those that are capable responders, and many think that these are like the primary complex of tuberculosis that gives tuberculin sensitisation. The point to debate is, might we not be killing such supposedly immunising infections by DDS? Medical ethics demand that we treat all cases of leprosy, but many of us do not indeed prescribe dapsone at the first sign of a lesion in a child, but rather wait and observe. We see a majority of the lesions heal without treatment. Of course such liberty can be allowed only when the surveillance is very thorough, and is generally difficult in a mass programme. While not debating the limited utility in selective situations, screening the subjects by Mitsuda testing perhaps will be a more logical approach. A child refusing to be Mitsuda positive after three tests in a year could be safely considered under risk, and needs to be protected if exposed to infection in the family or the community.

Age and sex patterns in leprosy—It has always been said that children are the most susceptible, and that females are generally more resistant than the males. Carefully collected records in a prospective study however do not support either of these views. Chatterjee has analysed some old and new data from centres that had kept good records (2), and from these it became apparent that children are not the most susceptible. Infection by many pathogens do not always lead to clinical disease. In endemic areas where chances of getting infected are very high, we do not see many established or progressive disease in children. The below table showing the conversion rate of clinically doubtful lesions and acid-fast bacillary skin positives, to established cases show clearly a progressive decline of resistence with advancing age.

However leprosy in children is a very important index of intravillage active transmission, and the child rate falls at a rather slow rate compared to the adults. One of the best ways of ascertaining whether a village has foci of transmission is to look searchingly, but without arousing suspicion, at the bare bodies of the children that invariably cluster about you when you visit a village, for lesions of leprosy.

On sex distribution of leprosy, I would quote an interesting passage from the third survey report of the leprosy investigation centre, Bankura, by Dharmendra & Sen (3), 1943. "Of the 29 cases, 15 were males and 14 femels. The sex distribution of these cases is different from the sex distribution of the cases recorded in the original survey........ this difference .... has possibly been caused by the fact that during the two year period under review a lady doctor worked in the area for more than three months, and detected the majority of the new cases reported in the females. It is *believed* (emphasis is mine) that the lady doctor detected a number of previously undetected cases in females, and the finding in these two years are not

TABLE

*DEVELOPMENT OF CLINICAL LEPROSY AT SURVEY II AMONG OBSERVATION CASES & SKIN-CLIPPING POSITIVES OF SY I

	Observation cases				Skin-clipping AFB positives			
Age Group	Total Examd.	Cases	Obsrvn. Months	Incidence Rate % per year	Total Examd.	Cases	Obsrvn. Months	Incidence Rate % per year
0-14	21	2	256	9.4	97	6	1342	5.4
15-44	40	11	503	26.2	113	13	1574	9.9
45 & above	18	6	219	32.9	32	9	434	24.9
All age Groups	79	19	978	23.3	242	28	3350	10.0

* Data reproduced from records of Leprosy Field Research Unit, Jhalda.

interpreted to mean that the incidence in the two sexes in this area is nearly equal. This however shows the necessity of great caution in interpreting the figure for the sex distribution of cases obtained in surveys carried out exclusively by male doctors". The inherent message is clear. In the assessment survey of the Santhal Pahadia Seva Mandal referred to earlier, we designed a 'parts examined' check list, and the paramedical worker was required to check the parts that were, or could be examined. In the parts of the body like face, back, legs, & upper extremities, the rate of distribution of lesions did not vary between the males & females, but when it came to the front (breast), buttocks & thighs, a majority of females' check list were returned as 'not examined', and females with diagnostic lesions in these parts were no doubt left undiagnosed. In our Jhalda study, we have employed equal numbers of male & female para-medical workers, and there is very little male-female disparity in leprosy rate. Ganapati, Nayak and Pandya (4), in their studies on leprosy in school children in Bombay observed—"one cannot but be struck by the significant proportion of cases (252 out of 953 or 26.4%) with solitary lesions on the gluteal regions and the thighs. The importance of careful examination of these parts of the body can not be overemphasized. Lesions have come to light in several instances by stripping the child to expose the waist and upper parts of the buttocks properly". This further strengthens the point made about sex disparity. However the females get less of lepromatous leprosy compared to males. Having learnt sex disparity as an artefact of inadequate examination of the female person, we have been seeing a disturbing trend of a persistence of the disease in the females parhaps due both to non-treatment, and a tendency to delayed healing. Females are not taking, or made to take treatment. In the villages, families are scared to expose their diseased females in public. A few that are conscious take clandestine treatment usually from quacks.

The lepromin test

A large number of laboratories and investigators around the world are engaged in a search for, and testing of *M. leprae* specific antigens. Leprosy infection in the armadillo first produced by Kirchheimer and Storrs (5) has proved a boon and it is now providing *M. leprae* in great quantities to laboratories and clinics that are involved in the IMMLEP programme of the WHO. A protein antigen has been isolated and its specificity tested in human subjects (6). It is worthwhile acknowledging with gratitude the pioneering work of Dr. Dharmendra's in the early forties (7) isolating a protein antigen from *M. leprae*, although due to inadequate purification and quantity, complete specificity of it could not be established at that time.

The usefulness of the two components of the lepromin test, namely the early, 24-48 hrs tuberculin type delayed hypersensitivity reaction of Fernandez', and the late reaction of Mitsuda's peaking at 3 weeks or longer, has been repeatedly confirmed. The early reaction is an indication of specific sensitization and is rarely if ever positive in individuals in leprosy non-endemic areas. The Mitsuda reaction however is non-specific; the proportion of positive reactors increases with age in any population and is unrelated to leprosy prevalence. Polar forms of lepromatous leprosy (LL) patients rarely become Mitsuda positive even if complete bacteriological negativity is achieved with treatment although many resolved cases often show varying degrees of Fernandez' reaction. Therefore, the nature of response and their significance are different for the two tests. While the Fernandez' reaction indicates sensitization, a positive Mitsuda reaction indicates an individual's capacity to be sensitized and to respond immunologically. Quite often a single test dose of lepromin confers positivity to a child (8) and on retesting after some weeks, a positive response is obtained. This phenomenon has been very effectively used for prognostication in a field study by Dharmendra and Chatterjee (9). In a highly endemic area of Bankura district of Bengal 803 persons were lepromin tested (age—sex not provided by the authors). Only 680 of the original group were available for examination on resurvey 15 or 20 years later. The lepromin test results of the 680 were:

Negative : —	156	
Positive : —	524	
	(Weak (W)	—163)
	(Moderate (M)	—125)
	(Strong (S)	—236)

109 of the 156 negatives were given 3 lepromin tests in one year to convert to

positivity. 93 of them were converted (W — 30, M — 35, S — 28), 16 remained negative.

A survey for leprosy 'incidence' in this population done after 15 or 20 years showed:

Lepromin response on first testing:	No.	Leprom.	Non-leprom.	Total
—ve	156	15(9.6%)	7(4.4%)	22(14.0%)
+ve W—	163	—	9(5.5%)	9(5.5%)
M—	125	—	3(2.4%)	3(2.4%)
S —	236	—	5(2.1%)	5(2.1%)
	680	15(2.2%)	24(3.5%)	39(5.7%)

Breake-up of the 156 original negatives showed:

Lepromin response	No.	Lep-rom	Non-leprom.	Total
—ve on one test (were not retested)	47	6	3	9(19%)
—ve on three tests	16	8	2	10(60.25%)
+ve after three tests	93	1	4	5(5. 4%)

Therefore, none out of 534 that were Mitsuda positive on first test developed lepromatous leprosy, and only 17 developed non-lepromatous leprosy. While 8 out of the 16 that remained Mitsuda negative after three tests developed lepromatous disease (50%).

A genetic susceptibility trait in the total non-responders could probably be responsible, and this test could be profitably used for screening out of the susceptibles. Rapid developments in the immunology have provided us with sophisticated laboratory tools for precise estimation of the hosts' capacity to respond immunologically to *M. leprae.* However, these tests are usually beyond the scope of routine application in the field except for research. Using a cellular immunological technique called the leprosy prognostic test (LPT), Barbieri and Correa (10) demonstrated that the ability of the hosts' macrophages to digest *M. leprae,* and their positive Mitsuda reactivity, were comparable. Further evidence on the great prognostic significance of the Mitsuda response has come from another recent report from Price et al (11) where the authors could not find any insufficiency of cellular immunity in none of 20 family contacts of leprosy tested. However, the 2 out of 20 that did develop definite lepromatous and borderline lepromatous leprosy, were Mitsuda negative. Confirmation of these findings by other groups of investigators seem to be of utmost importance since that would establish lepromin as a very effective and simple test to screen out a large proportion of the infected that become Fernandez positive on the one hand, and the susceptibles that remain Mitsuda negative on the other. The later group would be the one requiring attention and protection by (i) surveillance; (ii) immunization leading to Mitsuda conversion using B.C.G., lepromin or leprosy specific antigen (hopefully not far off in developing), failing which, (iii) chemoprophylaxis.

Viability and Persistence of M. leprae and Release from Isolation—The concept that only solid staining *M. leprae* are viable and the non-solid and granulated ones are degenerated and dead has come under increasing criticism from different quarters. However there are still many important leprosy workers who believe and defend it. This topic has been dealt with in detail in other articles in this volume. Perhaps it would be useful to discuss a little an alternative concept, the concept of a life cycle in *M. leprae,* that explains how *M. leprae* could become granular and still remain viable.

The fact that all eubacteriales including mycobacteria undergo varied morphological changes under diverse environmental influences is not very well recognised or appreciated. This is probably because direct observational (microscopic) studies of bacteria under different cultural conditions have not been quite popular of late. Environmental influences in test tube culture that brings about changes in bacterial morphology and consequently growth and metabolism are high salt concentrations, ageing, antibiotic and chemotherapeutic agents, and cell-wall attacking enzymes. The most widely studied abnormal morphological forms produced in artificial culture are the L-forms of bacteria induced mostly by Penicillin. The L-forms are partially or totally devoid of the cell wall, and have various pleomorphic, and filtrable forms. L-form transformation of pathogenic bacteria has also been observed in the diseased host and has been related to latency in infectious diseases. The most convincing evidence of this occuring has been provided by Wittler *et al* (12, 13). A corynebacterium associated with bacterial endocarditis would disappear from blood while under penicillin

therapy, leading to clinical remission, to reappear again with clinical relapse after pencillin was withdrawn. During the clinical and bacteriological intermissions, a pleomorphic organism, identified as the L-form variant of the corynebacterium associated with the clinical disease, and reversible to the parent organism, could be isolated from the blood of the child. Ultimately the infection was contained with an autogenous vaccine prepared from the corynebacterium, and valve surgery performed. Even after complete recovery, the L-forms persisted in the blood and the infection remained latent but presumbaly the antibodies produced in response to the specific vaccine prevented re-emergence of the intact organisms with cell wall, and consequently clinical disease.

Host substances that favour L-form transformation of an infectious bacterial organism are serum antibodies, complement and lysozyme, and lysosomal hydrolases that can attack and digest bacterial cell wall. Individuals suffering from lepromatous or near-lepromatous leprosy have all these ingredients present in their system in abundance, and *M. leprae* is an intracellular parasite residing and growing within macrophages. It is no wonder therefore that *M. leprae* will preferentially grow as L-forms in the diseased host. This it indeed does and the non-solid staining, granulated organisms, the acid-fast granules (? Much's granules), the globi and other abnormal morphological forms are all the result of continuous onslaught of the humoral immune substances, and macrophage enzymes on the cell wall of *M. leprae*.

It is now fairly well established that the ENL reaction of lepromatous & borderline lepromatous leprosy is due to tissue deposition of circulating immune-complexes, i.e. *M. leprae* antigens, antibodies and complement, causing an Arthus type reaction, with vasculitis. More of these circulating immune complexes are associated with ENL in these patients than otherwise. It has been observed that the bacteria in skin smears preceeding and during an ENL reactional episode become almost wholly fragmented, and also that the bacteria within the ENL lesion itself are also highly fragmented. It is very likely that this change in bacterial morphology is brought about by the immune substances, i.e. antibodies & complement, attacking the cell wall of the organisms. ENL reactions occur notoriously after initiation of treatment but can also occur in untreated patients, or in patients taken off treatment due to reactions. Therefore, the fragmentation of bacilli in reaction is unrelated to treatment. Treatment with DDS or other anti-leprosy drugs accelerates this process. The non-solid but intact organisms are not only not dead, they are destined to multiply in the L-form cycle which is far more efficient than binary fission; each of the four granules in a normal rod is potentially capable of growing into a globus generating scores to hundreds of rods within them.

Pleomorphism in *M. leprae* has been reported by Alexander-Jackson (14) and Xalabarder (15). Chatterjee (17) reported development of L-forms of *M. leprae* under test tube conditions and described the cycle, the various forms associated with it including the classical globus, and their significance. Pares, as reported by Pattyn (18), confirmed it independantly of Chatterjee. The granular transformation and decline and disappearence of solid staining rods as reflected in the morphological index (MI) has to be viewed in this context. While it might indicate that the treatment is being effective, it is no indication of bacterial death. Desikan (19) has obtained footpad multiplication from inocula that contained no solid staining rods. Another Indian investigator obtained foot pad multiplication from samples that did not have anything stainable, but he did not want to be identified.

Perhaps the key to the phenomenon of persistence of *M. leprae* in different tissues in cases under treatment with DDS, or even Rifampicin, lies also in the L-form phenomenon. Mostly these bacteria were still senstitive to the drug. The plausible explanation to this paradox seems to be their existence as L-forms, lacking a cell-wall, and therefore insensitive to the drugs. Browne (20) was perhaps the first to report on *M. leprae* persistence in cases apparently successfully treated and speculated on the possibility of L-forms bringing this about. Localised bacilliferous lesions containing very large numbers of good, solid bacilli would suddenly appear in patients undergoing treatment and apparently responding to it. The bacilli in at least four out of five such cases were still susceptible to DDS.

What then would be the criteria of releasing a patient from isolation? I use release here to mean the stage of recovery, bacteriological & clinical, when the patient will be certified safe to others, i.e. he ceases to be an active leprosy transmitter. This is important

because a child patient has to join school, an employee or a worker has to resume his work or he loses income or job, and a member of the family or community has to be able to freely mix, and the clinician has to certify him fit for that. The criteria set forth by the government would keep a lepromatous patient isolated for a very long time because attainment of total bacteriological negativity takes years, and further, a lepromatous patient is never to be discharged from therapy (WHO). This has meant loss of home, education and job to thousands and it is high time we evolve a rational policy that is scientifically acceptable, and easy on the patient. Quite opposed to the conservative recommendation of complete negativity, another strong view is that a patient ceases to be infectious when his skin smears show no solid staining rod, i.e. when the Morphological Index reaches zero. In the preceding section, the unsoundness of this advocacy has been dealt with, in the light of L-form life cycle in *M. leprae*. As is well known, untreated lepromatous patients often present with a 0% M.I. at first examination. Would we then declare this patient non-infectious before treatment was ever initiated? Obviously not, and the situation is not quite as simple. On an open trial on low doses of DDS in lepromatous leprosy, Karat (21) reported "While the morphological index in the majority steadily came down to zero and remained around that level during the follow-up period, the bacterial index showed either no significant change or an increase from the initial value was recorded". Accepting only the solid staining bacilli as viable, here is a peculiar situation where the viable ones were dying, and the dead ones multiplying. So, the M.I., in all probability, is no guide to success of therapy as manifested in bacterial death.

In the interest of the patients, the family and the community, we have to arrive at a decision, may be a compromise. Because waiting for clear cut answers for vindication of one or the other point of view may unfortunately be a long one, at least until we can cultivate *M. leprae* in the test tube. I would like to suggest the following guideline for discharge from isolation:

(1) Steady clinical and bacteriological improvement as reflected in a declining bacteriological index, following initiation of treatment with a suitable two drugs regimen;

(2) a negative nose;

(3) absence of globi in skin smears indicating a cessation of active bacterial multiplication;

(4) cessation of reactions, if any.

These conditions should continue to obtain for full one year, without reversal, before a patient should be declared non-infectious. After such certification, the patient will have to be kept under continuous clinical and bacteriological surveillance with 3 monthly check up until complete clinical resolution and bacteriological negativity of the skin is attained. At this point cases that may show signs of immunological recovery by converting into Mitsuda positivity of any degree can be gradually taken off treatment. The total non-responders are the ones that still need to be kept under continued therapy, with periodic Mitsuda testing to monitor possible immunological recovery, and smear examination of nose and/or sites showing clinical signs of re-activation.

This guideline may be considered not quite 100% safe but since a vast majority of the population and close contacts escape disease even after living the life time exposed to infection, any risk of transmission following this line of approach should not be very great, at least in endemic countries.

Drug Resistence in M. leprae

DDS resistant *M. leprae* as confirmed by the mouse foot pad technique, and suspected clinically for a long time, has been reported from various countries including India. It has understandably given rise to lot of concern in all quarters. Intermittent intake of DDS and low dosage have been held responsible. It has not however been generally appreciated that basically it is neither DDS nor *M. leprae* that is at fault. Most bacterial species contain in their populations mutants in various frequencies that are genetically resistant to one or the other inimical influences, be it drugs, chemical poisons or physical forces. The drugs only exert a selective influence, particularly when used in low dosage. While the mouse foot-pad model has been a very useful laboratory tool helping in many ways our understanding of the disease, it may have inadvertently done a dis-service by recommending a very low dose of DDS as the minimal effective blood level. The disease in the human, and the experimental disease

in the mouse, even in the immune-deficient mouse are very different in terms of quantitative bacteriology, or rather bacillary load. Unfortunately, the two have been equated, and hence the 'homeopathic' dosage recommendation of DDS, helping the emergence of bacilli resistant to it, which probably would not have surfaced with such frightening spectre if the orthodox dose would not have been disfavoured. It is indeed surprising that it took nearly two decades for DDS resistance to emerge as a clinical and control problem. This only indicates that resistant mutants are not present in the wild population in high frequency, and with judicious application of a multiple drug regimen at least at initiation of therapy, it could be brought under control before it gets out of hand.

Leprosy Control

From what has been said in the preceding few pages it is obvious that more laboratory studies and field trials are necessary to evolve a better method of leprosy control both to reduce transmission through mass treatment, and to give primary protection through immunisation. The screening of the susceptibles by immunological skin testing, reducing the load of the clinics by keeping single patch lesions under surveillance only, finding out the most economical, simple and field-usable multiple drug combination, making health education more effective to remove wrong social and administrative attitudes to enhance case detection & treatment through voluntary reporting, are all areas that need concentrated laboratory, field and administrative effort. Naturally abolishing the vertical Leprosy Control Programme at this stage of still insufficient scientific and operational knowledge will be most inopportune. Undoubtedly there has been serious alround lapses in the implementation of the programme but one cannot ignore the fact that leprosy consciousness in the population has grown even in rural areas where control activity has been extended. Other benefits and impact of the control programme have been discussed at length in other articles. From eradication of malaria, we are now learning to live with it because we diluted the emphasis on the programme rather too soon. Let us not repeat this mistake in leprosy control at a time when we are poised for a breakthrough in different areas of the problem.

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